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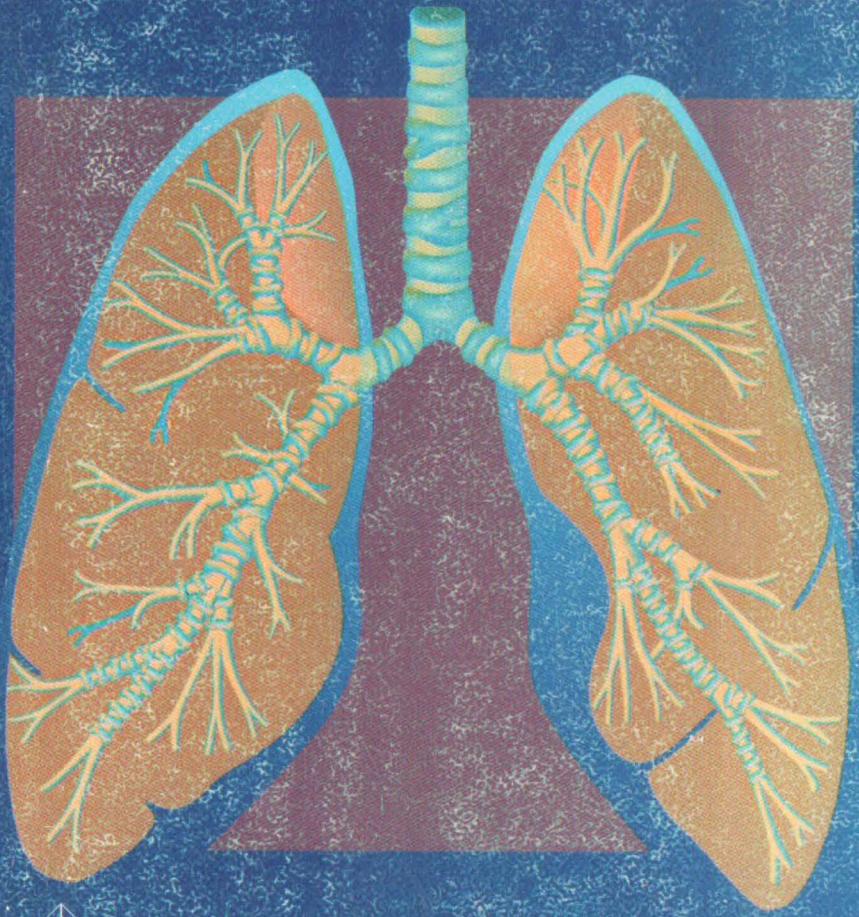
Manual of clinical Problems in Pulmonary Medicine

Fifth Edition

Edited by
Richard A. Bordow
Andrew L. Ries
Timothy A. Morris



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MANUAL OF CLINICAL PROBLEMS IN PULMONARY MEDICINE

FIFTH EDITION

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To

Kenneth M. Moser, M.D.

Healer
Mentor
Friend

This book is dedicated to the memory of Kenneth Miles Moser
("KM" to his students and colleagues),
a man of principle and vision, with an uncanny ability
to illuminate complex concepts for his students.
He was attentive and supportive to all
who were lucky enough to come under his tutelage, and
inspired each of us to "reach for the stars."
In gratitude for his tireless efforts,
we endeavor to carry on his mission of education.

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PREFACE

Nearly 20 years have passed since the publication of the first edition of the *Manual of Clinical Problems in Pulmonary Medicine*. That edition required almost three years from inception to publication, and its success set the stage for the ensuing editions. Now, we issue the fifth edition and, to our great regret, our teacher and inspiration, Dr. Kenneth Moser, is no longer with us. He is deeply missed. In his honor, all proceeds from the sale of this manual will be donated to the Kenneth M. Moser Fellowship Endowment established at UCSD. Dr. Moser always considered the Fellowship Program his "crown jewel." This, in our small way, is an opportunity for us to thank him, to express our appreciation for the guidance and support that meant so much to so many, and to follow Dr. Moser's example by contributing to the training of future leaders in our field.

Thanks to the internet, E-mail, and other joys of the electronic revolution, we have cut the development time by at least 50% from our previous editions. We hope that, with this edition, we present a compendium of the most current, authoritative, and well-referenced chapters pertaining to the 109 subjects selected. As has been our practice since the first edition, we have removed some of the older chapters and added new ones. Once again, we thank our dedicated group of contributors who have helped to produce this "Y2K" version in record time.

Finally, I thank my "new" co-editors, Andy Ries and Tim Morris, for the vast quantum of plain hard work that it took to organize and produce this manual. I am sure that K.M. would be proud of the result and comforted that future editions are in good and caring hands that will capture the spirit and quality of this manual—and this man.

RAB

ACKNOWLEDGMENTS

This book would not have been possible without the generous support and hard work of members and friends of the Division of Pulmonary and Critical Care Medicine at the University of California, San Diego (UCSD). Their commitment to this process has been unflagging since its inception. Our editors, Joyce-Rachel John and Lisa Consoli of Lippincott Williams & Wilkins, have quite simply been a delight; their humor and perspective helped us to find equilibrium during this sometimes exasperating process. We thank them for their guidance and patience. This project was administered and maintained mostly by E-mail, regular phone conferences, and a web site that we created. Remarkably, with everyone's cooperation, this book of many authors took less than a year from inception to completion. To Lela Prewitt and Cheryl Nelson, who assisted with the myriad administrative details, we owe a debt of gratitude. Our appreciation also to Richard Baron and Jim Baum and to Drs. Richard Stern, Risa Kagan, and Carolyn Ray for their valued counsel during this project.

Most importantly, we offer our personal thanks and love to Liz, Vivian, and Prudy for their constant support, understanding, and encouragement during the many early mornings and late nights we spent preparing this manuscript. We are grateful for these and countless other acts of support throughout our careers.

I. PULMONARY DIAGNOSTIC TECHNIQUES

1. RADIOGRAPHIC EVALUATION OF LUNG DISEASE

Paul J. Friedman

Chest radiography has provided noninvasive information about patients' anatomy and pathology for more than 100 years. The standard technique uses a cassette or dedicated chest unit with intensifying screens to record the x-ray image and lightboxes for looking at the films. Traditional methods are slowly being replaced by electronic imaging, computer manipulation, distribution of data via networks, and viewing of images and reports on computer workstations. [Newer imaging modalities such as computed tomography (CT) and magnetic resonance imaging are discussed in Chapter 2.]

Radiography is invaluable in the assessment of most lung and many heart diseases. The effective use of the chest film or other techniques, however, depends on combining clinical information with anticipation of the potential study findings. Knowledge of the limitations and costs of imaging modalities is also essential.

When a patient is considered for a chest radiograph, the clinician should have in mind as specific a question as possible and should convey that question to the radiologist in order to get the most constructive and useful interpretation. Imaginative variations on the routine chest study offer advantages that are rarely appreciated. Selection of other studies always requires communication between the chest physician and radiologist. Chest physicians also should be aware that the most valuable study to complement an abnormal chest film is an old chest film.

Technique

Standard chest films are made at a 6-foot distance (from x-ray tube to film), in posteroanterior (PA) and left lateral projections (left side against the film holder). The patient is instructed to take a maximal inspiration and hold it; normally, no attempt is made to control whether the patient maintains total lung capacity with the glottis open or closed. The film-screen combination should have a wide latitude and high sensitivity to limit the contrast of the image and the radiation dose. Using high kilovoltage, above 120 kilovolt peak (kVp), which makes it possible to show findings in the lungs and the mediastinum on the same radiographic film, enhances both benefits. High-kilovoltage radiography with a fixed grid to absorb the scatter is, therefore, the technique of choice. Supplementary methods, such as beam-shaping filters (to intensify mediastinal radiation) and intensifying screens and film emulsions with high and low sensitivity (to increase latitude), are also available.

Portable or bedside examinations, despite their greater cost and lesser quality, constitute a large part of chest radiography. They are more difficult to interpret because of shallow inspiration, which crowds normal parenchymal shadows together to simulate either infiltration or interstitial abnormalities; low kilovoltage technique, which can result in overexposed lungs and an underexposed mediastinum; and geometric distortion, because of the short tube-film distance. Because of the apical lordotic tilt of the x-ray beam, the diaphragm obscures a considerable portion of the lower lobe. The anteroposterior projection and short tube-film distance geometrically magnify the heart, which also obscures part of the lungs. In the supine position, pleural fluid and the pneumothorax are more difficult to detect, but on a semierect film the lung bases are crowded, simulating disease or effusion. It is important to avoid overinterpretation of portable studies, particularly those of poor quality.

Fluoroscopy of the chest is infrequently used to assess dynamic function. The method acquired a bad reputation when it was used promiscuously earlier in the modern era. Now it serves mainly as a guide to special procedures or as a means of localizing a lesion seen on only one radiographic view. However, diaphragmatic paralysis, mediastinal shift from air trapping, and tracheobronchial collapse can be detected with fluoroscopy. Determining whether a small pulmonary nodule contains calcium

can often be accomplished at fluoroscopy simply by positioning the patient for filming to minimize the superimposition of bones and vessels.

Nonroutine Radiographic Studies

Apical lordotic views are used in the assessment of localized lesions obscured by the clavicle and first rib. Tilting the thorax or the x-ray tube to project those anterior structures upward enhances visibility of lesions in the posterior segment of the upper lobes. The apical lordotic projection is not useful for lesions above the level of the clavicle or for anterior pathology. With the high-kilovoltage technique, the bones are much less opaque than they would be with old-fashioned nongrid techniques (70–100 kVp). Hence, this view is seldom used anymore.

Oblique views were used formerly to assess cardiac chambers, but are now useful mainly to provide additional tangential projections of the pleura, as in screening for asbestos plaques. These views can also be used to extend the routine examination when abnormalities are in the costophrenic sulcus or superimposed on the hilar shadows. Stereo views are essentially shallow obliques with a vertical shift between exposures. They were particularly useful in separating confluent shadows. Their use essentially has been abandoned.

Lateral decubitus views are probably overused. In the case of pleural disease, they have a dual capability: to show that an effusion is free (not loculated or organized) by layering when it is dependent; and to reveal whether the otherwise obscured lung expands normally when it is nondependent. The decubitus view is named according to the dependent side. The study is often misused to see if large effusions are free (or *layer out*). The real clinical issue with large effusions is whether and where to put the needle or chest tube, not whether the fluid is free. It may require special studies, such as ultrasound or CT, to show where to get at the fluid. In the bedridden patient, fluid levels in lung abscesses or pleural pockets can be shown best with the decubitus position, because it requires a horizontal x-ray beam to show an air-fluid level. This position is also good for the detection of pneumothorax on the nondependent side in patients who cannot assume the upright position. The decubitus position also makes it possible to test for diaphragmatic mobility by inducing a deep inspiration in the nondependent lung in an uncooperative patient.

An expiratory film is usually used to detect a small pneumothorax, because it is known that the apparent size of the pleural air collection will be larger when the lung is more collapsed. This procedure is not recommended for two reasons: (a) a pneumothorax so small as to be visible only on an expiratory film is not clinically significant; and (b) the expiratory film cannot be compared with prior or subsequent inspiratory studies to see if the patient is getting better or worse. A dynamic expiratory film to test for mediastinal shift or more subtle findings caused by air trapping requires an x-ray exposure before the end of full expiration and restoration of equilibrium. Similarly, a forced expiration, or Valsalva maneuver, will cause a reduction in the size of pulmonary vessels and systemic veins compared with a routine study and can be used to help distinguish them from nodes.

Conventional tomography is no longer used in facilities that have computed tomography, because both mediastinal and hilar abnormalities are better displayed and diagnosed with CT. Tomography works by blurring radiographic shadows outside a selected plane. Linear tomography was the method of choice for the lungs; pluridirectional tomography was better for the main bronchi and hilar regions, but required special apparatus.

Digital Chest Radiography

The pattern of x-rays that emerges from the body has traditionally been captured on intensifying screens and transferred directly to film. The developed film negative is what we look at on a light box. For about a decade, there has been increasing use of phosphor plates to receive the x-ray image, with electronic detection or read-out. The image can then be printed on film (hard copy) using a copy machine, or alternatively, can be read from the screen of a networked computer (so-called *soft copy*). Detail resolution has improved so that it is now almost comparable to conventional radiography.

This technique has been most popular for bedside radiography, because portable films are often technically poor; the computer interface allows adjustment of image density, and because the portable films were already limited in resolution, no significant degradation of quality is seen in digitized images. For situations in which a dedicated chest unit can be used, a newer modality is being developed: direct digital radiography. With it, the image is formed on a radiation-sensitive screen in the apparatus and scanned out to a computer network. Various materials and techniques are under development. Viewing is more likely to be on a computer monitor, but printing of film is possible, although costly.

One interesting feature is the ability to make images at different x-ray energies, so that it is possible to separate the high atomic number (i.e., calcium) materials in the image by calculation. Bone and soft tissue images can be separated, enhancing the possibility of showing lung lesions without superimposed ribs and detecting calcium in pulmonary nodules. In general, nodule detection is superior because of computer enhancement of the image. Computer networks and archives for images, or PACS (Picture Archiving and Communications System), are an important but costly advance in making images accessible to all, eliminating lost films, improving retrieval of comparison films, and speeding up the radiologic interpretation of current images.

Screening

The exception to the concept of carefully planned radiography is the screening examination. Large screening surveys for tuberculosis have been shown to be ineffective with current prevalence rates, although institutions still use routine films for pregnant women who have positive tuberculin skin tests or have not been tested before delivery, and some states require films for teachers or food handlers. Screening films for tuberculosis can also be justified in patients in whom skin tests are unreliable (e.g., those with acquired immune deficiency syndrome). Usually, just a PA view is sufficient.

Screening for occupational lung disease is a well-established practice and has epidemiologic and clinical utility. An elaborate system of classification of pneumoconiosis-related changes in the lungs and pleura has been developed for the International Labour Organization (ILO), and a network of readers qualified by examination is maintained by the National Institute of Occupational Safety and Health (NIOSH). No findings are available on occupational asthma, however.

Screening for lung cancer has been studied extensively; its efficacy can be expressed in terms of the cost per operable lung cancer discovered or, more significantly, per additional 5-year survivor. Recent studies have raised the question of whether early detection of lung cancer actually increases survival or merely brings the patient to care earlier in the course of the disease without lengthening the patient's life span. This means that 5-year survival after detection may be a meaningful measure in a neoplasm which shortens life expectancy markedly (e.g. lung cancer), whereas mean survival following detection is not. Whereas systematic screening of high-risk groups, therefore, is of debatable but measurable utility, a routine annual chest film as part of an annual physical examination is of essentially no value. See Chapter 2 for a discussion of chest CT in lung cancer screening.

Another controversial screening application is the routine admission chest film. Patients with no history or findings related to the heart or lungs are not likely to show abnormalities. Similarly, a routine preoperative screening chest film has low efficacy in patients without clinical evidence of heart or lung abnormalities. A tendency exists to obtain only a PA projection when screening. This practice is acceptable, but it should be understood that any patient in whom there is suspicion of abnormality of the heart or lungs should have a lateral view as well. The cost-containment-motivated abandonment of most lateral films in Great Britain should be deplored.

Error

Radiologic evaluation of the chest is accompanied, unfortunately, by a significant rate of error. Studies of the detection of even well-defined abnormalities (e.g., lung cancer) have shown an average false-negative rate in the range of 30% to 40%. Part of the error

may be attributed to failure to detect lesions against the background complexity of normal anatomy and, in part, to errors in interpreting whether shadows are significant. It has been shown that the likelihood of making a correct diagnosis from the film is enhanced by having an appropriate clinical history and also that the best improvement in error rate is achieved by independent double reading of films, with adjudication of differing interpretations. For these reasons, to maximize accuracy, the primary physician and radiologist should study chest films both independently and in consultation.

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2. SPECIAL PROCEDURES IN CHEST RADIOLOGY

Paul J. Friedman

Imaging-based procedures of the chest include computed tomography (CT), high resolution CT (HRCT), magnetic resonance imaging (MRI), diagnostic and interventional ultrasonography, bronchography, bronchial arteriography and embolization, aortography, and percutaneous biopsy or fluid drainage with imaging control.

Computed tomography is a reliable way to study nearly all abnormalities of the lungs, pleura, and mediastinum. Because CT shows cross-sectional anatomy with high contrast resolution, it has inherent advantages over plain radiographic techniques (a) in showing the shapes of structures without superimposition and (b) in distinguishing fat, cystic, or solid tissues. Its sensitivity for pulmonary nodules or interstitial disease is greater than that of the plain film. Intravenous contrast material helps distinguish vessels from other soft tissue structures in the hila and mediastinum (e.g., nodes, tumor). CT has replaced radiographic tomography of the lungs and mediastinum.

New scanners can scan continuously while the patient is moved, so-called *helical* or *spiral* scanning, allowing a complete scan during the arterial phase of an intravenous injection. Ability to capture the entire lung without the registration errors inherent in multiple breathholds is valuable. The newest scanners use multiple detectors to allow collection of up to four simultaneous images, further accelerating the production of data. This makes low-cost CT screening of the entire lung on a single inspiration possible, which changes the economics of screening for lung cancer in high-risk populations. Another consequence of helical scanning is the production of a volume of data, which can be reformatted accurately in any plane, with three-dimensional displays under development; these include CT angiography and virtual bronchoscopy.

Computed tomography can be used to explain abnormal mediastinal contours seen on plain chest films and to detect enlarged lymph nodes in the staging of lung cancer. Unfortunately, no significant density differences are seen between nodes enlarged by inflammation or by tumor. CT angiography of the pulmonary arteries is a new, moderately effective technique for detecting pulmonary embolism. Its sensitivity drops off in subsegmental vessels, but it is useful in patients with abnormalities that would *a priori* render a nuclear scan indeterminate.

Computed tomography is unsurpassed for studying the pleural space. Fluid collections are readily distinguished from masses or organized pleural tissues, and from consolidated lung, sometimes difficult with ultrasound. Pleural air collections can be distinguished from lung abscess cavities more easily than on chest films. Pleural fibrosis and plaques can be detected and distinguished from extrapleural fat most readily on CT.

High resolution CT of the lungs is a rapidly growing application. The "HR" refers to the high (er) resolution that results from narrower collimation than conventional CT, plus the use of an edge-enhancing reconstruction algorithm. Instead of consecutive 7- to 10-mm thick slices of the lungs, HRCT uses 1- or 1.5-mm thick slices, with interslice spacing appropriate to sampling rather than complete coverage of the lungs (as would be required in excluding metastatic disease). The thinner slice reduces volume averaging that would obscure lung detail. The sharper image reconstruction algorithm should be provided for all lung images.

Inflammatory diseases that are invisible on chest radiographs can be seen with HRCT, including bronchitis, bronchiectasis, early interstitial infiltration, miliary disease, or minimal alveolar filling. HRCT findings are often more diagnostically specific than those on the chest film as well. Emphysema can be detected with greater accuracy than is reflected in abnormal pulmonary function tests and can be quantitated for comparative studies. Studies of the lungs for bronchial abnormalities, interstitial lung diseases, miliary disease, or emphysema are best done using HRCT (without contrast material).

Magnetic resonance imaging is used only to a limited extent in diseases of the heart, lungs, and mediastinum. Technically, it should be understood that MRI does not

depend on ionizing radiation, but on the magnetic properties of atoms, notably the most abundant—hydrogen. The molecular environment of these atoms affects the rate at which they can dissipate energy, and this energy is converted into a spatial distribution of image densities, using mathematical reconstruction techniques similar to those used in CT. Successful use of MRI in the chest requires cardiac gating because image acquisition time is more than one cardiac cycle, and the heart motion shakes the nearby lung and mediastinum.

Magnetic resonance imaging has lost its advantage over CT in the production of sagittal and coronal (or oblique) images because helical CT scanning use is widespread. CT angiography now competes directly with MR angiography, both usually using contrast material, but otherwise noninvasive. MRI is still regarded as the gold standard for cardiac chamber volume measurements, especially for the geometrically irregular right ventricle. It is the most accurate, although complex, method of measuring the ejection fraction of that chamber.

Calcium is invisible on MR scans, so radiographic techniques (including CT) cannot be completely replaced in studying the mediastinum. The soft tissue specificity of MRI is greater than that of CT, however. MRI has an important application in the assessment of direct invasion of the chest wall or mediastinum by lung cancer.

Ultrasonography has been used for many years by radiologists and chest physicians to localize pleural fluid and to guide drainage procedures. Less widely used applications include transbronchial examination of the mediastinum to localize lymph nodes (for biopsy) and transthoracic detection of pulmonary nodules at the time of thoracoscopic biopsy or excision. Transesophageal ultrasound is of some value in diagnosing mediastinal masses seen on chest film, as well as providing excellent delineation of cardiac valves and flow velocities. The physical principle of ultrasound imaging is the production of echoes to the ping of a piezoelectric crystal transducer by tissue planes; the delay in the echo is converted into a distance, and a whole set of data is transformed into a cross section of anatomy. Three-dimensional ultrasound is a new technique that has not been used in chest disease except for experimental work in the heart.

Bronchography is an archaic technique for evaluating the morphology of the bronchial tree. Its major indication was in the preoperative assessment of bronchiectasis distribution, but HRCT has become the standard for this purpose and in the workup of hemoptysis. Evaluation of central bronchial abnormalities is more directly performed by fiberoptic bronchoscopy, although *virtual bronchoscopy* by three-dimensional reconstruction of noncontrast CT images is being developed.

Selective bronchial arteriography is useful to identify and treat by embolization enlarged bronchial arteries causing hemorrhage in patients with chronic infection. This is a very specialized procedure, requiring knowledge of anatomic variations of the bronchial and spinal arteries. The principal complication of embolization, aside from failure to control bleeding, is accidental embolization of a spinal artery, with spinal cord damage.

Aortography has been used to help analyze abnormal mediastinal contours and to exclude traumatic or dissecting aneurysms. CT and MRI are comparable in diagnostic efficacy, although CT is usually avoided to prevent toxicity from a double dose of contrast material if an aortogram will likely be necessary in preoperative assessment. In chronic situations, CT or MRI angiography is preferred. In acute situations, aortography should be used without hesitation.

Percutaneous lung biopsy under fluoroscopic control is discussed in Chapter 8, but lesions too small or too central to be safely needled under the fluoroscope can be biopsied successfully using CT control. Mediastinal nodes can be approached percutaneously with the help of CT or transbronchially with ultrasound. New, faster multidetector CT scanners offer a *fluoroscopic* mode of several axial views per second, which greatly speeds up the whole process.

The subspecialty of interventional radiology is routinely used for percutaneous catheter drainage of pus from various body sites, including the pleural space. Most fluid collections can be drained using ultrasound guidance, but complex cases often require CT, both to establish the anatomic location of the fluid and to help direct the catheter safely. CT fluoroscopy can speed this procedure. Loculations in a fluid collection, however, can be detected only by sonography. Percutaneous drainage of lung

abscess may be considered for patients who cannot control their secretions, to avoid soiling other parts of the lung, or when the abscess is contiguous to an empyema or thickened pleura.

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3. PULMONARY FUNCTION TESTING

Jack L. Clausen

The pulmonary function laboratory is a valuable resource for the diagnosis and management of patients with disorders affecting the respiratory system. Pulmonary function testing serves multiple clinical purposes. It can (a) uncover clinically undetected dysfunction and disease; (b) diagnose and characterize the type of dysfunction; (c) evaluate objectively the physiologic severity of disease; and (d) monitor the response to therapeutic interventions. The utility of pulmonary function testing varies according to the technical and clinical expertise of the personnel performing the studies. In addition, optimal equipment and techniques of testing, accurate measurements and data reduction, and selection of appropriate normal predictive data are essential.

Because of the wide range of normal values observed for most pulmonary function tests (PFT), it is essential to narrow the predicted *normal* range for a given patient, if *normal* is to be distinguished from *abnormal* with any degree of precision. This distinction may be achieved by using regression equations based on physiologic parameters such as age, height, and sex. For some PFT, weight, race, and altitude of the testing laboratory can also be important. Published series for predicted normal values are numerous. Suggested references are listed in Table 3.1.

Predicted values for some pulmonary function parameters differ by race which, in part, may be secondary to cultural differences in nutrition. Optimal correction factors are controversial and not well defined. For African-Americans, the American Thoracic Society recommendation is to reduce white-predicted values for vital capacity (VC), TLC, and 1-second forced expiratory volume (FEV_1) by 12%. Predictive values for residual volume (RV), functional residual capacity (FRC), and instantaneous flows (e.g., forced expiratory flow [FEF] 50%) are reduced by 7%. For Asians, the issue of race correction is more complex and involves to a greater degree the subject's nutritional history; in our laboratory, we generally use a 7% reduction for VC, TLC, and FEV_1 for Asians.

For many PFT parameters (e.g., VC and FEV_1), predictive values for a given patient calculated from equations from different published studies are generally similar. For other tests (e.g., single-breath diffusing capacity for carbon monoxide [DLCO], instantaneous maximal expiratory flows, Pa_{O_2}), predictive values derived from different equations can differ significantly. For such parameters, it is important that each laboratory evaluate its testing methodology and choice of predicted normal values by comparing measured values in normal subjects (n = 10–20) with the normal predictive values selected. If a greater number of normal subjects have test results outside the limits of

Table 3.1. Suggested references for normal values

Test	References[a]
Spirometry	8, 9, 12
Flow-volume	10,
Lung volumes (RV, FRC, TLC)	11,12
DLCO	15, 16
Pa_{O_2} Pa_{CO_2}, pH	14
MIP/MEP	13

TLC, total lung capacity; Pa_{O_2}, arterial oxygen tension; DLCO, carbon monoxide, diffusing capacity; MIP, maximum inspiratory pressure.

[a] Numbers refer to references at the end of this chapter.

normal than expected, then both the testing methodology and choice of predictive values need to be checked. The choice between different prediction equations can be identified from the study that produces the lowest sum of residuals.

The clinical significance of PFT results for an individual patient often requires an appreciation of the lower limits of normalcy. Although the mean −1.96 SD (two-tailed t-test, $P < 0.05$) is a commonly used statistical criterion, the mean −1.65 SD (one-tailed t-test, $P < 0.05$) is a more appropriate lower or upper limit of normal for most clinical purposes. For some parameters in which the data are not distributed normally, the lower limits must be defined either by normalizing the regression equation or by observing the actual upper and lower percentile values taken from a large population. Exact identification of the limits of normalcy for a specific patient is most readily accomplished using computer-developed reports that use the specific limits of normalcy from each prediction equation. Approximate lower limits of normal (95th percentile) are presented in Table 3.2.

Because results from patients with mild disease can widely overlap the range of predicted normal values, for borderline-low results (e.g., 90th percentile) it is often best to interpret such results as being consistent with either mild disease or normal function (*low-normal*). Such a conclusion may suggest the need for further testing if clinically indicated.

Despite the most rigorous efforts to predict optimal normal values, a relatively wide range of normalcy is still found for most PFT parameters. Hence, the most useful predictive values in an individual patient are baseline measurements made when the patient was free of disease.

Table 3.2. Approximate upper and lower limits of normal at the fifth percentile level

Parameter	Limits of normal
VC, FVC	75
FRC	70, 130
RV	65, 135
TLC	80, 120
FEV_1	75
FEV_1/FVC (%)	85
FEF 25/75	65
MIP	65

VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; FEV_1, one-second forced expiratory volume; FVC, forced vital capacity; FEF, forced expiratory flow; MIP, maximum inspiratory pressure.

Logical selection of appropriate PFT is essential for obtaining the maximal clinical information without unnecessary overuse of healthcare resources. A variety of tests are available; selection should be based on the clinical problem being evaluated. A survey of the available tests and their potential applications follows.

Spirometry can be used to measure the inspiratory and expiratory flow rates (Fig. 3.1). It allows assessment of certain lung volumes (i.e., tidal volume, expiratory reserve volume, inspiratory capacity, and VC) (Fig. 3.2). Simple spirometry can usually differentiate obstructive from restrictive pulmonary disorders by measuring VC and expiratory flow rates. In obstructive disorders, spirometry demonstrates a decrease in flow rates and a normal or decreased VC. Asthma, chronic bronchitis, and emphysema are the most common obstructive diseases; obstruction can also result from a localized lesion (e.g., a tumor, foreign body, granulation tissue, or scarring) anywhere in the tracheobronchial tree.

A large number of processes cause restrictive lung diseases (conditions that reduce TLC). This complicated differential diagnosis can be simplified into five basic pathophysiologic categories (summarized by the mnemonic PAINT): pleural disease, alveolar, interstitial, neuromuscular weakness involving ventilatory muscles, and thoracic cage abnormalities (e.g., kyphoscoliosis, obesity).

In restrictive diseases, spirometry usually demonstrates a decrease in VC and normal or increased ratio of FEV_1 to forced vital capacity (FVC). Instantaneous flow rates may be reduced solely because of the reduction of absolute lung volumes in the absence of any identifiable causes of obstructive airway disease (Fig. 3.3). Spirometry alone, however, cannot identify the presence of restrictive disorders when a patient has combined obstructive and restrictive disorders; in such patients, direct measurements of TLC are needed to identify and quantify the degree of restriction.

The FEV measured during the first second of VC (FEV_1) is the most reproducible flow parameter and is particularly useful in the diagnosis and monitoring of response to therapy in patients with obstructive disease. The FEF measured during expiration of 25% to 75% of the VC (FEF 25% to 75%), previously called *maximum mid expiratory flow rate*, may be more sensitive than the FEV_1 to detect mild dysfunction of the small airways, but the long-term clinical significance of this dysfunction is uncertain. The broader range of normal values for FEF 25% to 75% and instantaneous flows such as FEF 50% and FEF 75% also limits the clinical usefulness of these parameters.

Spirometry performed before and after exercise is useful for confirming the diagnosis of exercise-induced asthma. In patients undergoing evaluation for hypersensitivity lung disease (bronchospastic or restrictive), physiologic testing after inhalation of cholinergic agents or of the suspected antigenic material is often useful in identifying a specific cause. In addition to serial measurements of VC and expiratory flow rates (and airway resistance or specific conductance, if available), temperature and white blood cell count should be monitored following antigen inhalation.

In contrast to the spirogram, which measures volume versus time, the flow-volume loop (Figs. 3-1 and 3-3) displays flow rates as they relate to lung volume during a maximum inspiration from RV and maximum expiration from TLC. The principal advantage of the flow-volume loop is that the relationship of flows to lung volume is more readily recognized. Although marked blunting of peak flows and the resultant square loop shape of flow-volume loops are commonly taught to be characteristic of localized obstruction of upper airways (e.g., as occurs in tracheal stenosis), it is important to note that these are relatively insensitive signs of localized obstruction and, when present, usually signify severe localized obstruction (Fig. 3.4).

Gas dilution, or washout techniques, body plethysmography, and radiographic planimetry can be used to measure the absolute volumes of the lung (i.e., TLC, FRC, RV). In normal subjects, all three techniques give comparable results, but this is frequently not the case in patients with certain lung diseases. Gas dilution techniques (e.g., helium dilution, nitrogen washout) are the most commonly available methods for measuring absolute lung volume but often underestimate the true TLC in patients with obstructive disease, because they measure only the lung volume that communicates freely with the upper airways. Body plethysmography measures the compressible gas volume within the thorax and gives more accurate TLC measurements in chronic obstructive pulmonary disease, although under some conditions plethysmography

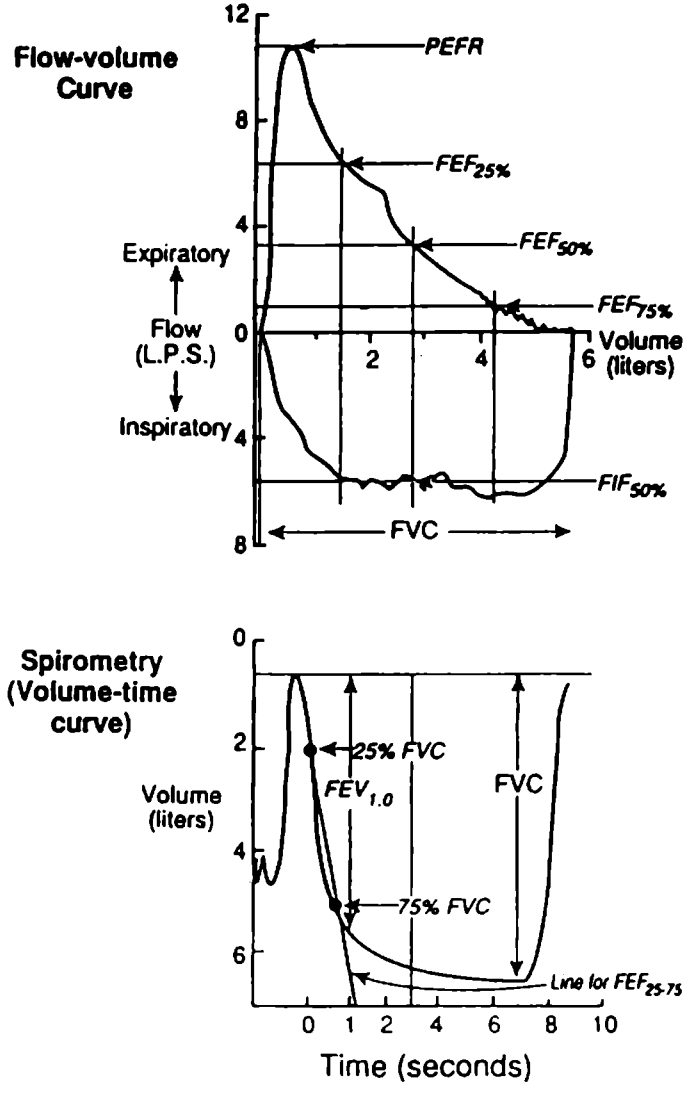

FIG. 3.1. Illustrations of measurements of forced vital capacity and maximal inspiratory and expiratory flow parameters from either flow-volume curves or volume-time curves. [Reproduced with permission from J Clausen. Pulmonary function testing, In: Kelley WN, ed. *Textbook of Internal Medicine.* 3rd ed. New York: Lippincott-Raven; 1997. (From: Comroe JH, Forster RE, DuBois AB, Briscoe WA, Carlsen E, Eds. *The Lung: Clinical Physiology and Pulmonary Function Tests.* 2nd ed. Chicago: Year Book Medical; 1962. Bloom NB, Hamilton LH. *Respiratory Physiology.* 3rd ed. St. Louis: Mosby; 1976.)]

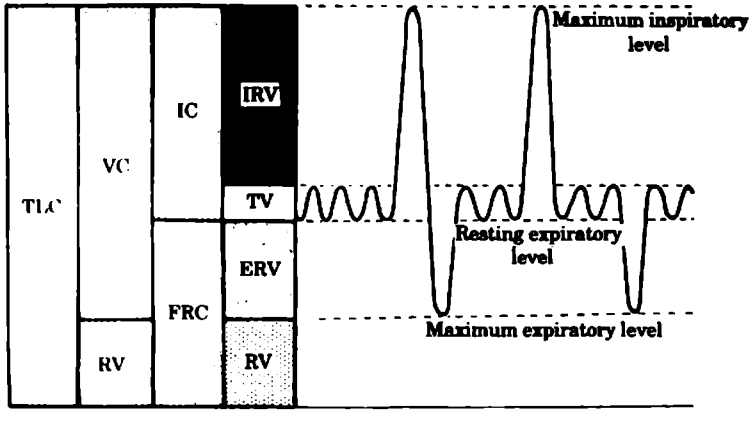

FIG. 3.2. The static lung volumes are derived from standard spirometry and from a measurement of functional residual capacity, either by body plethysmography or by gas dilution or washout. They include TLC (total lung capacity), VC (vital capacity), RV (residual volume), FRC (functional residual capacity), TV (tidal volume), IRV (inspiratory reserve volume), ERV (expiratory reserve volume), and IC (inspiratory capacity). (Reproduced with permission from Comroe Jr JH, et al. *The Lung: Clinical Physiology and Pulmonary Function Tests.* 2nd ed. Chicago: Year Book; 1962.

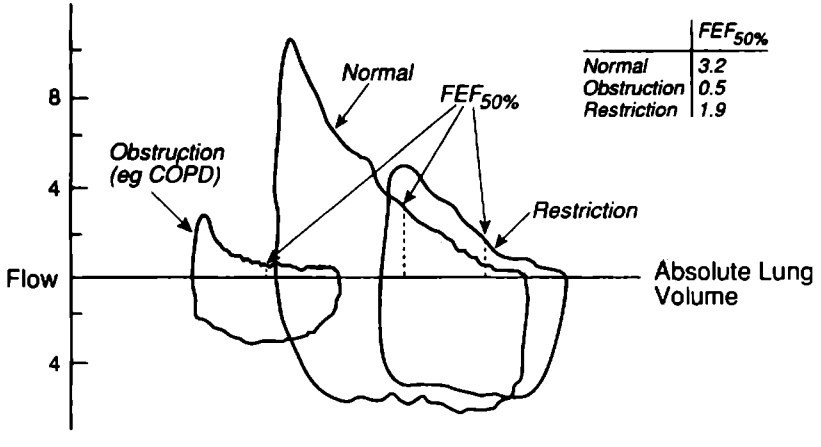

FIG. 3.3. Examples of flow-volume curves in obstructive and restrictive disease (flow-volume loops demonstrating normal, obstructive, and restrictive patterns). Although representing the same respiratory maneuver as the standard volume-time plot, the flow-volume loop provides a more graphic demonstration of the relationship of flow rates to lung volumes. Although flow rates referenced to forced vital capacity (FVC) are lower than normal in the patient with restriction, when referenced to the absolute lung volumes, the flows are actually higher than in a normal subject. [Reproduced with permission from Clausen J. Pulmonary function testing. In: Kelley WN, ed. *Textbook of Internal Medicine,* 3rd ed. New York: Lippincott-Raven; 1997. (From Slonim NB, Hamilton LH. *Respiratory Physiology.* 3rd ed. St. Louis: Mosby; 1976.)]

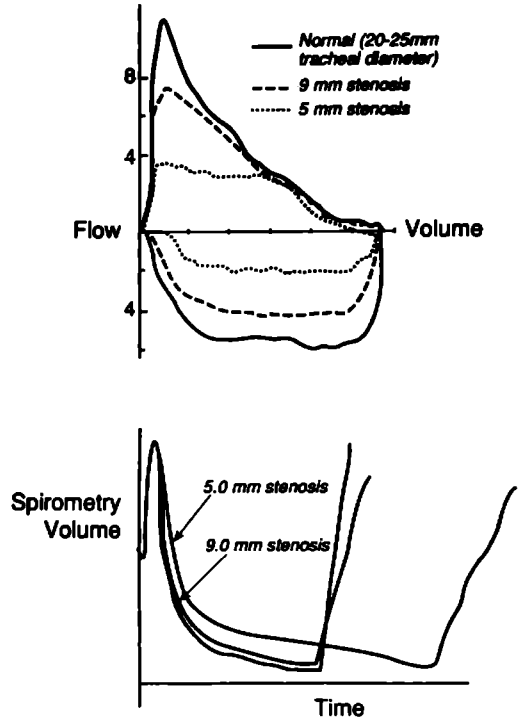

FIG. 3.4. Effects of different degrees of tracheal obstruction on volume-time and flow-volume displays. The squared loop characteristic of localized fixed obstruction of central airways (e.g., tracheal stenosis) is not apparent until the stenosis approaches a 9-mm diameter opening, and it is even more difficult to appreciate from volume-time displays. [Reproduced with permission from Clausen J. Pulmonary function testing. In: Kelley WN, ed. *Textbook of Internal Medicine*. 3rd ed. New York: Lippincott-Raven; 1997. (From Slonim NB, Hamilton LH. *Respiratory Physiology*. 3rd ed. St. Louis: Mosby; 1976.)]

may overestimate lung volumes in patients with severe obstruction. TLC can also be measured from conventional posteroanterior chest radiographs using planimetric or ellipsoid techniques; although averages of radiographic volumes from groups of normal subjects have shown remarkable correspondence to plethysmographically measured TLC, the accuracy of the measurements in individual patients can limit the clinical usefulness of these measurements to serial studies. In patients with severe reduction in lung volumes from space-occupying abnormalities, radiographic TLC can be significantly larger than plethysmographic measurements indicate. Assuming the patient has made an adequate effort (an oft overlooked assumption), a reduced TLC indicates the presence of a restrictive disorder.

Measurements of DLCO by either the single-breath or the steady-state method are often relatively sensitive, although nonspecific, indicators of respiratory dysfunction. Decreases in the single-breath DLCO correlate well with loss of lung tissue secondary to emphysema; however, in contrast with the steady-state method, the single-breath method occasionally gives false-negative results. Because of the wide range of normal values, both the single-breath and steady-state techniques are of limited usefulness

for early detection of emphysema. The DLCO is also reduced in a variety of restrictive diseases involving the lung parenchyma such as sarcoidosis, diffuse interstitial fibrosis, and bleomycin toxicity. It can also be low in pulmonary vascular diseases such as pulmonary embolus; hence, the specificity of the DLCO is low. The test may be most useful in the evaluation of a patient complaining of dyspnea who has essentially normal spirometry and arterial blood gases. In those patients, a low DLCO strongly suggests the presence of significant disease, although a normal DLCO does not exclude the presence of disease. Recent data also indicate that serial measurements of DLCO are useful in following patients with Goodpasture's syndrome, in which an occult pulmonary hemorrhage is mirrored by an increase in DLCO.

Measurements of the elastic recoil (ER) and static compliance (SC) of the lung require measuring changes in esophageal pressure obtained via an esophageal balloon and plotting these changes versus the corresponding changes in lung volume. The SC measures the ratio of the change in lung volume to the change in transpulmonary pressure—pressure required for lung inflation, or alveolar minus pleural pressure—during periods of no gas flow. The transpulmonary pressure measured at TLC reflects the ER of the lung and is useful for physiologically documenting pathologic alterations in lung elasticity in diseases such as sarcoidosis (increased ER) or emphysema (decreased ER). The wide range of reported normal values, however, significantly limits the sensitivity of the ER or SC for early detection of disease. The time required for these measurements and limited patient acceptance also prevent their use as screening procedures.

Closing volume, phase III slope, helium-oxygen studies, and assessments of dynamic compliance are tests that may be sensitive indicators of early small airways dysfunction. However, because these tests generally do not identify the patients whose disease will progress to clinically disabling obstructive lung disease, they now play a limited role in clinical practice.

Maximum inspiratory pressure is determined during maximum inspiratory effort against a closed system, usually at RV. It is a useful direct test of inspiratory muscle strength and should be evaluated in all patients with suspected neuromuscular disease or in those with dyspnea, restricted lung volumes, and an absence of parenchymal or thoracic cage abnormalities on chest roentgenograms.

Maximum inspiratory pressure is nonspecific in that it cannot distinguish among lack of effort, muscle weakness or dysfunction, and neural disease. Nonetheless, when the disease is present, the test is useful for following its course. Tests to assess respiratory muscle fatigue have improved but are too complex for widespread clinical use. The contributions of respiratory muscle fatigue to dyspnea and respiratory failure remain poorly defined.

Exercise testing is useful for diagnosis and assessment of dysfunction in patients with lung and heart disease (see Chapter 4). Its measured parameters include respiratory rate and tidal volumes, arterial blood gases, expired gas concentrations, and, frequently, heart rates and blood pressures. Abnormalities (e.g., hypoxemia or hypercapnia) can occur in patients who have normal function at rest. Exercise testing is invaluable in detecting lung dysfunction, in assessing the impact on exercise, in establishing the need for supplementary oxygen, and in assessing the impact of therapy, including rehabilitation programs for patients with chronic obstructive pulmonary disease.

Assessments of changes in FRC and flow limitation of tidal volumes during exercise can identify causes of dyspnea during exercise and exercise limitation not otherwise detected during conventional exercise testing. This testing is currently available in relatively few centers and its clinical usefulness remains to be fully defined. Assessing changes in tidal breathing flow-volume curves during the application of negative pressures can also be useful in identifying patients for whom airway collapse may play an important role in the genesis of dyspnea at rest or during exercise.

The development of pulse oximeters has clearly expanded the monitoring of oxygenation of patients in a variety of situations (e.g., during general anesthesia or during procedures such as bronchoscopy, and in intensive care units). Limitations, however, in the absolute accuracy of these devices for measuring the percent of oxygen saturation (±5%) limit the usefulness of these devices when accurate assessments of oxygenation are needed (e.g., determining the need for long-term ambulatory oxygen therapy, recognizing mild lung dysfunction by the detection of decreases in arterial oxygenation during exercise).

The causes of hypoxemia include hypoventilation, diffusion abnormalities, ventilation-perfusion mismatches, right-to-left shunts, and decreased oxygen in inspired gases. Gas exchange abnormalities leading to hypoxemia and hypercapnia occur as a result of (a) wasted ventilation, because lung units are ventilated but not perfused; (b) shunted pulmonary blood flow because lung units are perfused but not ventilated; and, more commonly, (c) other less extreme forms of ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. The alveolar-arterial oxygen difference ($P[A\text{-}a]O_2$) estimates the degree of shunt and *low* ($\dot{V}/\dot{Q}$) mismatch. More specific tests are available to quantify or define the topography of such mismatching within the lungs. Wasted ventilation can be calculated by determining the percentage of alveolar dead space (VD) per unit of tidal ventilation (VT) using the Bohr equation:

$$VD/VT = \frac{Paco_2 - PEco_2}{Paco_2}$$

where $PEco_2$ is the end-tidal expiratory concentration of carbon dioxide and $Paco_2$ is the arterial carbon dioxide concentration. An elevated VD/VT (>0.45), in the absence of restrictive or obstructive lung disease suggests vascular disease.

The degree of shunt can be assessed by determining the arterial oxygen tension (Pao_2) while the patient breathes 100% oxygen; this technique does not distinguish between an intracardiac and an intrapulmonary shunt. A Pao_2 of less than 550 mmHg suggests the presence of a shunt. However, resorptive atelectasis induced by breathing 100% oxygen may convert areas of low ($\dot{V}/\dot{Q}$) to apparent shunt. Quantitative information regarding the spectrum of ($\dot{V}/\dot{Q}$) mismatch can be derived by elegant but complicated multiple inert gas methods. So far, these methods remain a tool of the research laboratory. The topography of ($\dot{V}/\dot{Q}$) relationships can be displayed in a semiquantitative fashion by ventilation and perfusion scintiphotography.

The importance of disturbances of respiration during sleep is increasingly recognized. Comprehensive sleep studies, which include the ability to assess electromyographically and electroencephalographically defined stages of sleep and arousals, are important for understanding the relationship between disturbances of respiration and sleep, daytime fatigue, and excessive daytime sleepiness. However, the increasing availability of miniaturized, portable multichannel recorders has made available options much less expensive than full polysomnography for the detection of nocturnal desaturation, alterations in inspiratory airflow and ventilatory effort, and cardiac arrthymias which may occur only during sleep, with resultant impact on daytime function (see Chapter 77).

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4. EXERCISE

Andrew L. Ries

Exercise is a physiologic stimulus that stresses the body's capability to increase metabolic activity and gas transport, and to produce energy. Conditions that reduce reserve in organ function may be undetectable at rest and only manifest symptoms on exertion. Dyspnea on exertion is one of the most common complaints prompting patients to seek medical advice. Because dyspnea is a subjective symptom with diverse origins, evaluation during exercise can elicit symptoms and help characterize physiologic responses. In recent years, exercise testing has become more widely available to evaluate patients with pulmonary diseases.

Exercise testing can have several objectives:

1. Support a specific diagnosis
2. Assess an individual's work capacity and the factors limiting exercise tolerance
3. Evaluate changes with disease or the effects of therapeutic interventions
4. Determine the need for certain forms of therapy.

Differences are seen in the physiologic principles and in the appropriate techniques used for exercise testing of different populations, such as normal individuals, cardiac patients, and patients with pulmonary disease. These differences reflect the reason(s) for exercise limitation in each of these groups. Therefore, to be safe and informative, exercise testing must be planned with consideration of these limiting factors.

In the normal individual, maximal exercise is limited by the level to which cardiac output can be elevated and by the ability of the muscles to generate sufficient metabolic energy. No limitations are imposed by ventilatory reserves or pulmonary gas exchange, except with extreme exercise levels.

In normal subjects, low-level exercise results in an increase in cardiac output (primarily caused by an increase in heart rate), widening of the arterial-mixed venous oxygen difference ($(a\text{-}\bar{v})O_2$), and increase in oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Minute ventilation increases sufficiently to maintain the alveolar ventilation at a level great enough to remove all of the carbon dioxide produced; therefore, the $PaCO_2$ remains normal. The $P(A\text{-}a)O_2$ gradient can decrease slightly with exercise because of improvement in ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships as pulmonary blood flow increases and pulmonary perfusion becomes more evenly distributed.

As the exercise level is increased, the blood flow to the exercising muscles ultimately becomes inadequate to provide sufficient oxygen to maintain pure aerobic metabolism. At that point, anaerobic glycolytic metabolism occurs (*anaerobic threshold*). Lactic acid enters the venous circulation, is buffered by bicarbonate, and an additional amount of carbon dioxide is produced. In response to this nonoxidative carbon dioxide production, minute ventilation ($\dot{V}E$) rises disproportionately to the $\dot{V}O_2$—a signal that the anaerobic threshold has been reached. At higher exercise levels, lactic acidosis decreases the pH level sufficiently to drive $\dot{V}E$ higher, out of proportion to carbon dioxide production, causing a fall in $PaCO_2$.

This classic sequence of responses to exercise has been characterized carefully in normal subjects. For example, at lower aerobic levels of exercise, the physiologic variables reflecting increased metabolic demand are related closely (e.g., $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, heart rate, cardiac output, and $(a\text{-}\bar{v})O_2$). Exercise stress response patterns can help to detect abnormalities in patients with cardiac or pulmonary dysfunction. In patients with left ventricular failure and reduced stroke volume, for instance, the heart rate increases and the $(a\text{-}\bar{v})O_2$ difference widens more at a given level of $\dot{V}O_2$ than in normal subjects.

In patients with many lung diseases, the classic physiologic principles described in normals are not followed during exercise because pulmonary patients generally are not limited by hemodynamic capabilities but by ventilatory function, pulmonary gas exchange compromise, or both. Recent evidence suggests that peripheral muscle dysfunction also contributes to the limitations in maximal exercise tolerance in patients with chronic lung disease. Ventilatory limitations are imposed by factors such as disordered respiratory mechanics, an increase in the work of breathing, disturbances of $\dot{V}/\dot{Q}$ relationships (e.g., large dead space ventilation), and respiratory muscle fatigue. Gas exchange limitations may be a consequence of alveolar hypoventilation, shunting and right ventricular failure, or $\dot{V}/\dot{Q}$ imbalance. Because the limitation to exercise in many pulmonary patients is not of hemodynamic origin, the use of heart rate, for example, to guide *maximal exercise* or training targets is often not useful. Furthermore, many patients with moderate to severe lung disease may not achieve a definable anaerobic threshold because they are forced by dyspnea to discontinue exercise before this point is reached.

Thus, it is characteristic in pulmonary patients for exercise limitation to occur at $\dot{V}O_2$ and heart rate levels well below those predicted from nomograms developed in normal populations. Furthermore, to test exercise tolerance safely in pulmonary patients, it is important to monitor the arterial blood gases to avoid severe hypoxemia; hypoxemia is not a consequence of exercise in normal subjects, except at extreme levels of exertion.

The practical details of exercise testing in the pulmonary patient depend on the purpose for which such testing is done. For example, if the exercise testing is a prelude to developing an exercise program for a patient with chronic lung disease, testing is best accomplished on an apparatus (e.g., treadmill) that requires exercise comparable to that used during training (e.g., walking). This is because muscle conditioning is most specific for the type of exercise used in training and may not be transferable directly to another form of exercise. For example, tolerance for walking is not improved by training on a supine bicycle or by arm exercises.

The specific measurements made also depend on the purposes of the test. For instance, if the question relates to whether the patient requires supplementary oxygen during exercise, then measurement of arterial blood gases at rest and during exercise is necessary, and the exercise level should be appropriate to the patient's daily activities. Furthermore, if arterial hypoxemia appears with exercise, the test can be repeated with supplementary oxygen provided at a known flow rate, to ensure that the flow rate selected prevents hypoxemia.

Laboratory exercise testing is most commonly performed using either (a) rapid, progressive, incremental levels to a symptom-limited maximum or (b) defined steady-state levels. The former is most useful for determining exercise tolerance and the limitations to maximal performance. The latter may be preferred for assessing training prescriptions (e.g., heart rate target for endurance exercise) or for accurately measuring physiologic variables requiring a steady state (e.g., cardiac output or dead space ventilation). Simpler exercise tests (e.g., the 6-minute walk test) have been used increasingly in recent years to measure maximal exercise tolerance outside of a laboratory setting. These timed distance walk tests measure the maximal distance a person can walk within a defined time period (e.g., 6 minutes). Such tests have the advantage of requiring less equipment and technical expertise; however, attention must be paid to the details of testing procedures because variations in factors such as the walking course, patient instructions, encouragement during tests, use of oxygen or monitoring devices, and number of tests performed will influence the results. If these tests are to be used widely, then better standardization of procedures is needed. Also, these tests do not provide the detailed physiologic data typically included in more formal laboratory exercise tests.

Two common errors in using exercise tests in pulmonary patients are to assume that (a) normal arterial blood gas values at rest obviate the need for exercise measurements and (b) one can judge from resting pulmonary function and arterial blood gas testing that the patient will or will not have serious gas exchange deterioration with exercise. Neither of these assumptions is correct. Also, it is often difficult to relate a patient's report of dyspnea on exertion to his or her actual physiologic performance during exercise—not a surprising fact, because dyspnea, as pain, is a largely subjective sensation.

In exercise training for the pulmonary patient, another common error is to select target training levels that are too low. In normal subjects or cardiac patients, training levels are typically chosen at submaximal percentages (e.g., 60% to 70%) of maximal $\dot{V}O_2$ or heart rate. Many patients with chronic lung disease, however, are often ventilatory limited at low levels of exercise, which may be below their anaerobic threshold. Such individuals can sustain exercise levels at higher percentages of maximum (e.g., 90% or above)—although the absolute levels are low.

Exercise testing has become an increasingly important component of the diagnostic-management approach to the patient with pulmonary disease. Familiarity with the techniques employed and with the utility of the data derived is essential to proper patient care.

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5. RADIOISOTOPIC TECHNIQUES

Timothy A. Morris

Lung ventilation and perfusion ($\dot{V}/\dot{Q}$) scanning is a powerful tool for assessing regional pulmonary blood flow and ventilation. The most common clinical application of V/Q scanning is for diagnosing pulmonary embolism; the classic finding is a focal perfusion defect without a matching ventilation defect. Several promising alternative diagnostic techniques are being developed for the diagnosis of pulmonary embolism; however, radio-

isotopic lung scanning remains the most affordable noninvasive option. $\dot{V}/\dot{Q}$ scanning also has unique diagnostic properties that make it useful in several other clinical situations.

Perfusion scans are performed following injection of the radioisotope technetium 99m (Tc 99m), incorporated into particles of macroaggregated albumin (MAA) or human albumin microspheres (HAM). A typical dose of Tc 99m MAA for a Q scan contains 100,000 particles and 1 to 2 mCi of radioactivity. Because the individual particles are larger than the pulmonary capillary lumen, they become trapped in the lungs on the *first pass*. The focal Tc 99m-radioactivity intensity, therefore, reflects the proportional distribution (but not the absolute amount) of blood flow to each lung region. The capillary obstruction from the scan is harmless, because only 0.3% of the capillaries are affected and the albumin particles disintegrate within 8 hours.

Because the distribution of pulmonary blood flow is gravity-dependent, ideally, the radioisotope should be injected with the patient half in the supine and half in the prone position. Injecting in the sitting or standing position can lead to artifactual apical *defects* on the scan. Optimally, the perfusion scan should include at least six views: anterior, posterior, right and left lateral, and two oblique views.

Ventilation scanning can be performed with several different radiopharmaceuticals, either as a gas or as an aerosol. The most commonly used isotopic gas is xenon 133 (Xe 133). For ventilation scans, Xe 133 is mixed with air or with a suitable concentration of oxygen to obtain a dose of approximately 5 mCi/L. After several deep breaths of air, the patient is connected to a shielded spirometer containing the radioactive gas. Usually, an initial breath is taken to total lung capacity and recorded (single-breath scan). Next, the patient breathes tidally while the distribution of gas is recorded (wash-in phase). After the concentration of radioactivity has equilibrated between the patient's lung and spirometer (equilibrium phase), the patient resumes breathing room air (washout phase). Retention of the gas locally during the washout phase is the most sensitive finding for detecting ventilation abnormalities; this phase should be used for interpretation.

Aerosolized radiolabeled particles have become popular alternative agents for ventilation scans. The most widely used of these is Tc 99m diethylenetriamine penta-acetic acid (DTPA). Because it is an aerosol rather than a gas, Tc 99m DTPA distribution is determined by the mass and inertial properties of the particles as well as by the patterns of regional ventilation. Turbulent airflow in large airways can lead to deposition on bronchial walls, causing localized *hot spots* that complicate scan interpretation. Although they have some practical advantages, some ventilation scans performed with aerosolized Tc 99m particles yield different results than Xe 133 scans. Pertechnegas, consisting of very small (<1 μm) aerosolized Tc 99m-labeled carbon particles, avoids some of the disadvantages inherent to other radiolabeled particle ventilation scans. The small Pertechnegas particles travel to the alveoli without depositing on airway walls. Thus, less residual radioactivity is superimposed on perfusion images. It has yet to be determined whether the theoretical advantages of Pertechnegas will translate into improved diagnostic accuracy over more conventional (and less expensive) methods.

Although cost and efficiency considerations have led to the widespread use of aerosols, we prefer Xe 133 for diagnostic ventilation studies. In addition to the improved image characteristics, practical advantages are found with this method. Because of the differences in gamma emission *windows* between the two isotopes, the (Xe 133) ventilation scan can follow the (Tc 99m) perfusion scan without significant degradation of the ventilation images. The ventilation scan can be performed in this sequence in the view that optimally displays the perfusion defects; also, a normal perfusion scan makes ventilation scanning unnecessary, minimizing scanning cost and radiation exposure. Finally, aerosols do not provide a washout phase, and we have found that phase to be of diagnostic value in several clinical contexts.

The major application of perfusion and ventilation scans has been to exclude or confirm the diagnosis of pulmonary embolism. Multiple clinical trials defining the sensitivity and specificity of lung scans for pulmonary embolism make clear that the perfusion and ventilation tests should be considered separately. Interpreted alone, the sensitivity of the perfusion scan is extremely high. Indeed, a normal perfusion scan excludes the diagnosis of clinically significant embolism; that is, outcome studies have shown that withholding treatment in patients with a normal scan (and no venous thrombosis) is safe. However, abnormal perfusion scans are nonspecific. To enhance

specificity, three key collateral considerations can be invoked: (a) the size of the perfusion defect; (b) matching chest x-ray findings; and, if necessary, (c) corresponding ventilation scan findings. If the perfusion defects are seen in areas with infiltrates by chest x-ray or if all defects are subsegmental in size, the study is nondiagnostic and ventilation scanning will add little of diagnostic value. If one or more defects are segmental or larger, without corresponding chest x-ray findings, a ventilation scan is done. If the defect(s) ventilates abnormally, the scan is nondiagnostic; if normally, the scan is diagnostic of pulmonary arterial occlusion.

Depending on the patient population, normal perfusion scans will be found in 10% to 20% of suspected embolisms, diagnostic scans in 15% to 20%, and nondiagnostic studies in the remainder. Nondiagnostic studies, however, are associated with a significant incidence of embolism. Calling such nondiagnostic studies *intermediate* or *low* probability unfortunately may lull the physician into complacency and lead to serious management errors.

In patients with acute symptoms, the $\dot{V}/\dot{Q}$ scan indicating *pulmonary arterial obstruction* means acute pulmonary embolism in the overwhelming majority of patients. However, any process that blocks flow through pulmonary arteries can produce this pattern. Among such processes are chronic pulmonary thromboembolic disease (where the obstruction is caused, at least in part, by fibroblastic organization of a once-active thrombus), Takayasu's arteritis, fibrosing mediastinitis, primary tumors of the pulmonary arteries, pulmonary artery agenesis, and, rarely, invasion or compression of pulmonary arteries by tumors or other mediastinal components (e.g., aorta, lymph nodes).

Another application of ventilation and perfusion scans pertains to the decision to perform lung surgery in a patient with limited lung reserve. For example, in a patient being considered for lung resection for cancer or bronchiectasis or for bullectomy, the lung scan provides important regional information that spirometry and other function tests cannot. Specifically, it can define whether the proposed area of resection or bullectomy is a major contributor to the patient's overall ventilation or pulmonary blood flow. In these situations, it is helpful to perform *quantitative* scans, in which the proportion of counts from various lung regions (relative to the entire lung) are measured to determine their contribution to the total lung ventilation and perfusion. If, for example, a right lower lobe site of bronchiectasis is poorly ventilated and barely perfused, its removal will not significantly impair gas exchange function; indeed, it may even improve it. If, however, the lobe carries a large percentage of the total blood flow, its resection can have serious hemodynamic and gas exchange consequences. Thus, quantitative ventilation and perfusion scans provide topographic data that, along with indicators of global function such as spirometry, help complete the pulmonary assessment of the surgical candidate.

Ventilation and perfusion scanning also offers a means of noninvasively differentiating primary pulmonary hypertension (PPH) from large-vessel, chronic thromboembolic pulmonary hypertension (CTEPH). In PPH, perfusion scans are normal or demonstrate a *mottled* appearance; in CTEPH, multiple, segmental or larger perfusion defects are invariably present. It should be noted, however, that Q scan results in CTEPH often significantly underestimate the actual degree of angiographic obstruction. Patients with unexplained pulmonary hypertension and one or more segmental perfusion defects should undergo further workup, especially if the perfusion defects are mismatched (see Chapter 66).

Radioisotope techniques using thrombus-specific targeting agents have also been used, or are under study, for the detection of venous thrombi and pulmonary emboli. The prototype of such approaches, radiolabeled fibrinogen, is no longer available but had been of great value in epidemiologic studies of deep venous thrombosis. Of potentially greater diagnostic value are radiolabeled antibodies and other radiolabeled agents with high affinity for fibrin, platelet receptors, and other components of active thrombi. Radiolabeled antifibrin antibodies, for example, bind to sites on the surface of acute thrombi and allow them to be detected by gamma camera imaging. An important advantage these agents may have over other imaging modalities is the ability to distinguish acute thrombi from other causes of vascular obstruction. For example, intravascular *scars* in the deep veins or pulmonary arteries caused by prior (inactive) thromboembolic disease can be confused with acute thrombi on more conventional *anatomic* tests such as ultrasound imaging, $\dot{V}/\dot{Q}$ scanning, helical computed tomography, and

even contrast angiography. However, radiolabeled antibodies will bind to vascular lesions only if biological components of thrombosis are present. In addition, because the antibodies bind equally well to both deep vein thrombi and pulmonary emboli, both lesions can be imaged with a single test.

Gallium-67 (Ga 67) lung scanning has limited usefulness in pulmonary medicine. Following intravenous injection, Ga 67 accumulates in tissues with increased metabolic activity (e.g., neoplasm, inflammation). Although capable of detecting roentgenographically unapparent foci of disease, the clinical application of Ga 67 scanning is limited by its nonspecificity. Certain *niches* for Ga 67 lung scanning are still used by some clinicians. For example, in sarcoidosis, Ga 67 scanning is frequently positive and is used in some centers to follow the progression of this condition. Whether Ga 67 scanning can predict functional deterioration or response to therapy more accurately than more standard tests (e.g., chest roentgenogram, spirometry) remains inconclusive.

Finally, radiolabeled white blood cells have been used widely to detect the presence of abscesses in the lungs and solid organs. The technique is imprecise and usually used only if other means of diagnosing infection have failed.

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6. EVALUATION OF ARTERIAL BLOOD GASES AND ACID-BASE HOMEOSTASIS

Robert M. Smith

Arterial blood gas (ABG) measurements are invaluable in assessing the adequacy of pulmonary gas exchange, and the presence and severity of acid-base disturbances. However, these values cannot be interpreted in a vacuum. Proper interpretation of arterial oxygen tension (Pa_{O_2}) and arterial carbon dioxide tension (Pa_{CO_2}) and pH values

requires knowledge of the clinical state of the patient, the therapy being applied, and, frequently, other data such as the mixed venous oxygen saturation, hemoglobin concentration, and cardiac output.

Scrupulous attention must be directed at collecting, handling, and analyzing the arterial blood gas specimen. The technique of choice for routine analysis is direct radial artery puncture with a 20-gauge (or smaller) needle attached to a heparinized syringe. When repeated sampling is necessary, an indwelling arterial catheter can be inserted, but it must be carefully monitored for local complications such as infection, thrombus formation, occlusion of arterial flow, and distal microemboli. The radial or dorsalis pedis arteries are the preferred sites for monitoring, as the ulnar or posterior tibial arteries provide redundant circulation. The brachial and femoral arteries are less desirable but can be used when circumstances warrant.

The specimen should be collected without exposure to ambient air, usually by allowing arterial pressure to force blood into the syringe. Many devices have been designed specifically for this purpose and facilitate good sampling technique. Any bubbles introduced into the syringe during collection should be promptly expelled; the sample should be mixed to assure complete anticoagulation and placed in ice water. Analysis should take place within minutes using an instrument system that has been recently calibrated against commercially available standards for each blood gas electrode (Po_2, Pco_2, and pH). The electrodes and sampling chambers are maintained at 37°C, and the results must be corrected to the patient's body temperature if it is abnormal. Pao_2 and $Paco_2$ are expressed in units of pressure, typically as millimeters of mercury (mmHg) or kilopascal (kPa) (1 torr = 1 mmHg = 7.5 kPa).

The blood gas results often include calculations of oxygen saturation, bicarbonate, base excess or deficit, and alveolar-arterial oxygen difference. Accurate knowledge of the fraction of inspired oxygen (Fio_2) and an estimate of the respiratory exchange ratio (R or RER) are necessary to calculate the alveolar-arterial difference. All of these calculated values depend on accurate measurement of Po_2, Pco_2, and pH. The electrodes are extremely accurate when calibrated correctly (Po_2 and Pco_2 ± 2 torr, pH ± 0.01 units) and the calculated values are equally precise. A common misconception is that the calculated [Hco_3^-] value obtained from ABG analysis is less accurate than that returned from a chemistry laboratory. However, the assumptions made when [Hco_3^-] is measured from a sample of venous blood in a chemistry analyzer (e.g., assuming a level for the $Paco_2$) render that latter measurement less accurate when a respiratory disturbance is present.

Although it can be difficult in the presence of significant physiologic derangements, initial examination of an ABG should include consideration of its technical adequacy. A few simple rules can help: (a) any Po_2 above 48 is unlikely to have been collected from a venous sample; (b) the sum of the Pao_2 and $Paco_2$ should be less than 140 mmHg if the patient is breathing room air; and (c) in the absence of a primary metabolic disturbance, a rapid large change of the calculated bicarbonate by more than 5 mEq suggests an error in the $Paco_2$ or pH, or the presence of excessive amounts of heparin (an acid) in the collection syringe.

Oxygen

The normal value of Pao_2 decreases with age and is influenced by barometric pressure and, therefore, by altitude. A Pao_2 less than 80 mmHg would be considered abnormal at sea level for a young person. However, the expected value for Pao_2 in Denver (ambient barometric pressure = 625 mm) is only 80 mmHg, whereas 60 to 65 mmHg would be expected for older persons.

Only small amounts of oxygen are transported in solution in the plasma. The bulk of the oxygen carrying capacity of blood resides in hemoglobin contained in red blood cells. The relationship between Pao_2 and hemoglobin oxygen saturation (Sao_2) is defined by the sigmoidal oxyhemoglobin dissociation curve. That relationship is such that Sao_2 falls only minimally until the Pao_2 drops to 60 mmHg (corresponding to a Sao_2 of 90%) and then falls more rapidly with further drops in Pao_2. For this reason, efforts to elevate the Pao_2 above 60 to 65 mmHg rarely provide significant clinical benefit in the management of

hypoxemic patients. The dissociation curve is shifted to the right in acidosis and to the left in alkalosis so that a Pa_{O_2} of 60 and a pH of 7.30 will yield a saturation of 87.7%, whereas a Pa_{O_2} of 60 and pH of 7.50 will lead to an oxygen saturation of 93.4%.

Classification of the severity of hypoxemia based on Pa_{O_2} is arbitrary. A value of greater than 60 mmHg is usually indicative of mild hypoxemia, 45 to 59 mmHg is moderate, and below 45 mmHg is severe. The major causes of hypoxemia are (a) a decrease in the oxygen content of the inhaled gas (e.g., from reduced barometric pressure with altitude or a hypoxemic gas mixture); (b) global hypoventilation; (c) ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance; and (d) right-to-left shunt (intrapulmonary or intracardiac). A decreased mixed venous oxygen content, as can occur when cardiac output is severely reduced, does not typically cause hypoxemia, but will markedly worsen the effects of shunt or $\dot{V}/\dot{Q}$ imbalance. These mechanisms can be differentiated by calculation of the alveolar-arterial oxygen difference $(A\text{-}a)D_{O_2}$ using the simplified alveolar gas equation:

$$P_AO_2 = P_IO_2 - \frac{P_ACO_2}{R}$$

$$\text{where } R = \frac{\dot{V}CO_2}{\dot{V}O_2} \quad \text{and } (A-a)\,D_{O_2} = P_AO_2 - P_aO_2$$

The $(A\text{-}a)D_{O_2}$ (also known as the (A-a) gradient or the $(A\text{-}a)P_{O_2}$ difference) is normally less than 20 mmHg. Patients with hypoxemia caused by a decreased F_{IO_2} (e.g., altitude) or by hypoventilation have a normal $P(A\text{-}a)_{O_2}$, whereas the other processes lead to a widened $P(A\text{-}a)_{O_2}$. Characteristically, patients with hypoventilation or $\dot{V}/\dot{Q}$ mismatch show a 3 to 5 mmHg Pa_{O_2} rise for each 1% increment in F_{IO_2}; those with a shunt show less than 2 mmHg rise for each 1% increment in F_{IO_2}. An alternative to the $(A\text{-}a)D_{O_2}$ calculation are the $Pa_{O_2}:P_AO_2$ or $Pa_{O_2}:F_{IO_2}$ ratios; these values are easier to compute but are not entirely independent of changes in F_{IO_2}. Table 6.1 provides guidelines for assessing hypoxemia.

The pulse oximeter, which is a popular choice for monitoring oxygen saturation in patients, can reduce the number of ABG analyses required when following a patient on a ventilator or in respiratory failure. The accuracy of oximetry for estimating oxygen saturation is good (±3% to 5%), assuming no significant carboxyhemoglobin or methemoglobin. However, oximetry gives no information about alveolar ventilation or acid-base status.

Carbon Dioxide

The Pa_{CO_2} reflects the balance between carbon dioxide production and carbon dioxide elimination by ventilation. This is stated by the equation:

$$Pa_{CO_2} = \frac{K \times \dot{V}CO_2}{\dot{V}_A}$$

Where $\dot{V}CO_2$ = carbon dioxide production per minute, $\dot{V}_A$ = alveolar ventilation, and k is a constant. If $\dot{V}_A$ decreases, Pa_{CO_2} will rise (hypercapnia), whereas a rise in $\dot{V}_A$ will result in a fall in Pa_{CO_2} (hypocapnia).

The normal range for Pa_{CO_2} is 37 to 43 mmHg, regardless of age. Pa_{CO_2} values of 30 to 37 mmHg are regarded as mild hypocapnia, 26 to 29 mmHg as moderate, and below 25 mmHg as severe. Mild hypercapnia is in the 44 to 50 mmHg range; moderate,

Table 6.1. Guidelines for assessing hypoxemia

Status	$(A\text{-}a)DO_2$	Pa_{O_2}/P_AO_2	Pa_{O_2}/F_{IO_2}
Normal	5–20	>0.80	>500
Low $\dot{V}/\dot{Q}$	30–50	0.65–0.70	300–450
Shunt	>60	<0.55	<250

51 to 60 mmHg; and above 60 mmHg, severe. These numbers should also be compared with baseline values, as any sudden change of baseline carbon dioxide may portend a serious change in pulmonary function. It is helpful to distinguish hypercapnic conditions in which total ventilation is normal or increased with increased dead space ventilation (e.g., chronic obstructive airway disease) from those with diminished total ventilation (e.g., sedative overdose or neuromuscular disease).

Arterial pH and Acid-Base Homeostasis

Two major principles of physical chemistry govern our understanding of acid-base balance. The first principle is that dissociation constants describe the equilibrium between a weak acid (HA) and its conjugate base:

$$HA \leftrightarrow H^+ + A^- \quad \text{or expressed mathematically } K_A = \frac{[H^+][A^-]}{[HA]}$$

The primary buffer in blood is the carbonate-bicarbonate base pair. Carbon dioxide is hydrated to carbonic acid; this dissociates to bicarbonate and $[H^+]$ according to the relationship:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

$$pK = 6.1$$

Mathematically, this is expressed as

$$K = \frac{[H^+][HCO_3^-]}{[H_2CO_3]} \quad \text{or} \quad K = \frac{[H^+][HCO_3^-]}{[CO_2]}$$

Rearranging and supplying the correct constants gives the Henderson equation, whereas taking the negative log of each side and rearranging gives the Henderson-Hasselbach equation:

$$[H^+] = \frac{24[PCO_2]}{HCO_3} \qquad pH = 6.1 + \log\left[\frac{[HCO_3^-]}{0.03 \times PCO_2}\right]$$

Henderson Equation Henderson - Hasselbach Equation

Although pH is the usual form of reporting the ABG, it is useful to be able to readily convert logarithm-based pH units to $[H^+]$ in nanoequivalents per liter (nEq/L). A normal pH (between 7.37 and 7.43) converts to $[H^+]$ of 43 to 37 nEq/L. A change in pH of 1 unit corresponds to a tenfold change in concentration, and a 0.3 unit pH change corresponds to a twofold concentration change ($\log(10) = 1$, and $\log(2) = 0.3$). On this basis, it is easy to construct a conversion table even when a scientific calculator is not available (Table 6-2). This conversion permits easier calculation of acid-base relationships using the simplified Henderson formula. An elevation of blood pH (decrease in blood $[H^+]$ is called alkalemia, whereas a decrease in pH (increase in $[H^+]$) is called acidemia. A condition that leads to acidemia or alkalema is acidosis or alkalosis, respectively, but compensatory mechanisms can actually leave the patient with a normal pH.

The second principle that governs acid-base homeostasis is that a solution must contain equal numbers of positively and negatively charged ions. For biologic systems, this can be expressed as:

Total Cations – Total Anions = 0 or

$$[Na^+] + [K^+] - [Cl^-] - [HCO_3^-] - [A^-] - [\text{Unmeasured Anions}] = 0$$

$$140 + 4 - 102 - 25 - 15 - 2 = 0$$

The concentration of the unmeasured anions that are normally present (e.g., SO_4^{2-} or PO_4^{3-}) is only 1 to 3 mEq/L, and the $[H^+]$ concentration is so low relative to other charged species that it can be neglected. $[A^-]$ represents the base pairs of other weak acids in

Table 6.2. Conversion between pH and hydrogen ion concentration

Alkalemia		Acidemia	
pH	$[H^+]$ (nEq/L)	pH	$[H^+]$ (nEq/L)
8.00	10	7.30	50
7.90	12.5	7.20	63
7.80	16	7.10	79
7.70	20	7.00	100
7.60	25	6.90	125
7.50	32	6.80	160
Normal		Normal	
7.40	40	6.70	200

blood. These consist predominantly of charged amino acid residues on plasma proteins. The pK of these charged groups is typically 6.6 to 6.8, and so they are 90% dissociated at pH 7.4. The total concentration of these protein-based weak acids in blood (A_{TOT} in mEq/L) is 2.4 times the protein concentration (g/dl). Thus,

$$A^- = A_{TOT} \times 0.90 = [\text{protein g/dl}] \times 2.4 \times 0.90 \text{ (normal} = 11 - 16)$$

This equation allows calculation of $[A^-]$ and fosters an understanding of the effect of hypoproteinemia on its magnitude. This concept is also the basis for the more common calculation of the *anion gap* in which $[A^-]$ and $[K^+]$ are assumed to be constant. With that assumption, a shortened version of the equation is:

$$\text{Anion gap} = [Na^+] - [Cl^-] - [HCO_3^-] \text{ (normal range} = 10 - 15)$$

Here, increases in the anion gap above the normal range reflect the presence of unmeasured anions, but no provision exists for changes caused by hypoproteinemia or for changes in $[A^-]$ from pH (which changes the dissociation state of the buffer groups). Correct estimation of the amount of unmeasured anions in solution is essential, as an elevation indicates the presence of a metabolic acidosis.

As noted, the hydrogen ion concentration $[H^+]$ is controlled to a very narrow concentration range between 10 and 100 nEq/L. To maintain the $[H^+]$ within this range, acid generation must closely match acid elimination. This extremely low concentration range (six orders of magnitude less than that of most other electrolytes) is even more remarkable relative to those overall rates of acid production. More than 100 mEq of *fixed* nonvolatile acids (e.g., sulfates or phosphates) and approximately 13,000 mEq of volatile acid are generated daily as byproducts of metabolism. The kidney excretes nonvolatile acids, whereas the lungs eliminate the volatile acid load as CO_2 (equivalent to 200 ml/min).

Disorders that alter CO_2 elimination (i.e., ventilatory changes that effect $PaCO_2$) are reflected in the numerator of the Henderson equation. These are referred to as respiratory derangements of acid-base balance. Conversely, if the excretion of fixed acids slows or accelerates in relationship to production, or if the intake of acid or alkali is abnormal, a metabolic disturbance in acid-base balance is said to develop. These changes are largely reflected in the denominator of the Henderson equation.

If the bicarbonate-carbonate system were the only buffer in blood, then changes in pH as a result of acute changes in $PaCO_2$ should not cause any change in bicarbonate levels. However, the presence of other blood buffers with a pK that is different from that of bicarbonate means that changes in pH will generate or utilize $[H^+]$, with a resulting small change in $[HCO_3^-]$. The magnitudes of these changes in pH and in bicar-

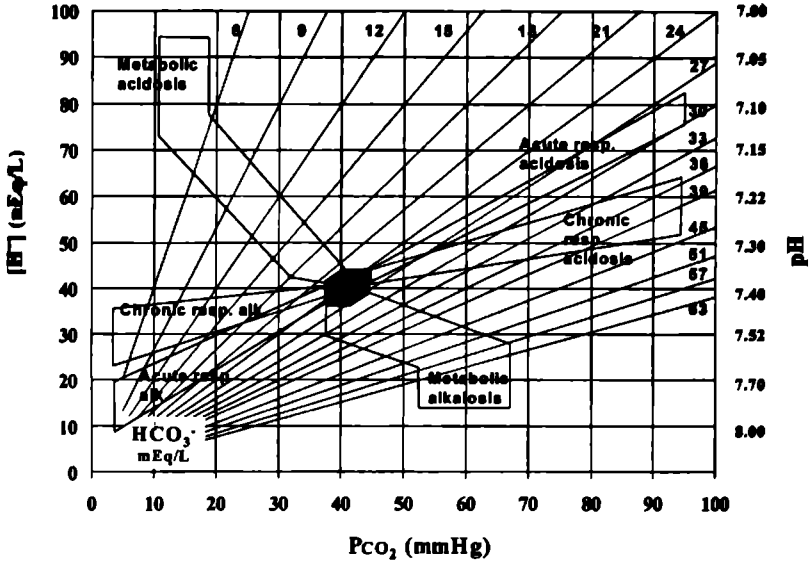

FIG. 6.1. Acid-base nomogram. The acid-base map provides insight into the type of acid-base disturbance (metabolic versus respiratory) and its duration (acute versus chronic). The dark lines represent the 95% bands for the predicted P_{aCO_2}, pH, and H^+ concentration in each simple disturbance. A point falling outside the confidence bands implies that the arterial blood gases cannot be explained by a simple disturbance alone (see text). Resp, respiratory; alk, alkalosis; N, normal. (Adopted from McCurdy DK. Mixed metabolic and respiratory acid-base disturbances: diagnosis and management. *Chest* 1972;62:35s.)

bonate as a result of acute changes in ventilation can be shown graphically (Fig. 6.1) or can be estimated from prediction equations (Table 6.3). For example, an elevation of P_{aCO_2} from 40 to 60 mmHg (an acute respiratory acidosis) produces a fall in pH (20 × 0.008) of 0.16 unit to 7.24, and a 2 mEq rise (0.1 × 20) in $[HCO_3^-]$. An acute respiratory alkalosis, characterized by a decrease in P_{aCO_2}, produces a rise in pH of the same magnitude as that in acute respiratory acidosis, but bicarbonate falls 0.2 mEq for every 1 mmHg decrease in P_{aCO_2}. The ability to predict pH and bicarbonate changes in response to ventilation is the basis for the concept of *base excess* and *base deficit*. Base excess (or deficit) is the difference between the measured bicarbonate and the bicarbonate level that would be predicted on the basis of the measured P_{CO_2} change alone. Base excess is often reported with the directly measured ABG results and can be useful as a means of estimating the metabolic processes that are present in combination with respiratory changes. However, the calculations assume normal values for electrolytes and serum protein that may not be valid. Thus, uncritical use of base excess or deficit values can lead to error.

The response to a chronic (more than several days) change in P_{aCO_2} is compensation through increased elimination or retention of bicarbonate by the kidney. These compensatory mechanisms act to restore the pH toward, but not quite to, normal values. The magnitudes of these compensatory metabolic changes are well established from clinical observation (Table 6.3 and Fig. 6.1). For every 10 mmHg elevation of P_{aCO_2} in chronic CO_2 retention, bicarbonate retention results in an increase in levels by

Table 6.3. Predicted changes in response to processes causing acidosis or alkalosis

Respiratory acidosis: (primary disorder: ↑ $Paco_2$ compensation: ↑ $[Hco_3^-]$)		
	Acute	Chronic
ΔpH	$-0.008 \times \Delta Pco_2$[a]	$-0.003 \times \Delta Pco_2$
ΔH^+	$0.8 \times \Delta Pco_2$	$0.3 \times \Delta Pco_2$
ΔHco_3^-	$0.1 \times \Delta Pco_2$	$0.4 \times \Delta Pco_2$
H^+	$0.8 \times Pco_2 + 8$	$0.3 \times Pco_2 + 27$
Respiratory alkalosis: (primary disorder: ↓ $Paco_2$ compensation: ↓ $[Hco_3^-]$)		
	Acute	Chronic
$\Delta pH =$	$-0.01 \times \Delta Pco_2$[a]	$-0.003 \times \Delta Pco_2$
$\Delta H^+ =$	$0.75 \times \Delta Pco_2$	$0.3 \times \Delta Pco_2$
$\Delta Hco_3^- =$	$0.2 \times Pco_2$	$0.5 \times \Delta Pco_2$
$H^+ =$	$0.75 \times Pco_2 + 10$	$0.3 \times Pco_2 + 28$
Metabolic acidosis: (primary disorder: ↓ $[Hco_3^-]$, compensation: ↓ $Paco_2$)		
$\Delta Pco_2 = 1.1–1.3 \times \Delta Hco_3$		
$Pco_2 = 1.5 \times [Hco_3] + 8$		
Pco_2 = last 2 digits of the pH		
Metabolic alkalosis: (primary disorder: ↑ $[Hco_3^-]$, compensation: ↑ $Paco_2$)		
$\Delta Pco_2 = 0.6–0.8 \times \Delta Hco_3$		
$Pco_2 = 0.7 \times [Hco_3] + 21$		

[a] Applicable for Pco_2 between 40 and 80 mmHg

4 mEq/L, blunting the pH change to 0.003 units for every 1 mmHg change in $Paco_2$. With chronic hyperventilation, renal bicarbonate elimination occurs until levels fall by 0.5 mEq for every 1 mmHg fall in $Paco_2$ with full compensation.

Metabolic acidosis and alkalosis occur when a primary disturbance occurs in the bicarbonate concentration of the blood. Respiratory responses occur to moderate the acidemia or alkalemia (Table 6.3 and Fig. 6.1). A quick rule of thumb is that the $Paco_2$ in response to a metabolic acidosis should equal the last two digits of the pH, although maximal respiratory compensation will only reduce the $Paco_2$ to 12 to 15 mmHg. If significant underlying respiratory disease is present, adequate compensation may not occur and the pH will be lower than anticipated. For example, a $Paco_2$ of 35 mmHg in the presence of a pH of 7.20 suggests an inadequate respiratory compensation caused either by underlying respiratory disease or by altered respiratory drive from a central nervous system process. With normal lungs, this would reduce an individual's $Paco_2$ to 20 mmHg. Significant hypoventilation ($Paco_2 > 45$) caused by metabolic alkalosis also occurs, but less consistently. The best "rule of thumb" in metabolic alkalosis is that $Paco_2$ rises by 0.7 for every 1 mEq rise in $[Hco_3^-]$.

When metabolic and respiratory processes have similar effects on pH, a mixed acid-base disturbance is said to exist. For instance, during cardiac arrest, respiratory acidosis and metabolic acidosis coexist in a combined acid-base disturbance, which results in a greater change in pH than expected from the $Paco_2$ changes alone. Combined metabolic and respiratory alkalosis can lead to marked elevation of pH with cardiac arrhythmia, fall in cardiac output, or seizures. In contrast, a mixed metabolic and respiratory disturbance exists when a process leading to acidosis is superimposed on an alkalosis, or vice versa. These are common in clinical practice and tend to be of somewhat less immediate

clinical impact because the pH tends to be closer to normal. For instance, patients with chronic respiratory acidosis from obstructive pulmonary disease will develop a compensatory metabolic alkalosis. If treated with corticosteroids or diuretics, they may develop a further metabolic alkalosis resulting in a normal or slightly alkalemic pH. One condition to be aware of is the mixed metabolic acidosis and respiratory alkalosis of salicylate intoxication. The characteristic pattern of low pH, elevated anion gap, and a lower $Paco_2$ than predicted from the compensation rules points to such a diagnosis.

Common conditions leading to acid-base derangements are listed in Table 6.4. In general, therapy should be directed at the underlying condition and not simply at correcting the pH toward a normal value.

To understand fully acid-base derangements, it is valuable to use a systematic approach to the analyses of the ABG results (Table 6.5). Most approaches begin by identifying any respiratory component to the derangement. If the entire abnormality is explained on the basis of the acute respiratory changes, then a primary respiratory disorder is said to be present. With change in $[HCO_3^-]$ beyond that predicted for an acute respiratory disturbance, is that change an appropriate compensation for a chronic respiratory disturbance? Metabolic compensation that is greater than the predicted value

Table 6.4. Common causes of disturbances of acid-base balance

Respiratory acidosis	Respiratory alkalosis
–Diminished ventilatory drive	–Catastrophic CNS event
–Sedatives	–Drug with direct stimulation of respiration (salicylates, progesterone)
–Central hypoventilation syndromes	–Sepsis (early)
–Severe CNS depression or injury	–Cirrhosis
–Diminished respiratory muscle function	–Pregnancy (third trimester)
–Guillain-Barré syndrome	–Decreased lung compliance (J receptor)
–Myasthênia gravis	–Anxiety
–Severe hypokalemia	
–Diminished pulmonary function	
–Chronic obstructive pulmonary disease	
–Status asthmaticus	
–Severe restrictive disease	
Metabolic acidosis	**Metabolic alkalosis**
With normal anion "gap"	–Hypochloremia (often with volume contraction)
GI bicarbonate loss	–Hypokalemia
Renal tubular acidosis	–Mineralocorticoid excess
Ureteral diversion	–Bartter's syndrome
NH_4Cl or HCl infusion	–Administration of alkali
Rehydration	–Compensation for respiratory acidosis
Hyperalimentation	
Compensation for respiratory, alkalosis	
With elevated anion "gap"	
Ketoacidosis	
Lactic acidosis	
Salicylate intoxication	
Methanol ingestion	
Ethylene glycol ingestion	

CNS, central nervous system.

Table 6.5. Approaches to the interpretation of blood gases

Step-by-step	"Quick and Dirty"
1. Is the patient acidemic or alkalemic?	1. Determine the predicted pH if all of the abnormality were due to changes in ventilation (i.e., if the P_{CO_2} were corrected to 40).
2. If the P_{CO_2} is abnormal, estimate whether an acute change in P_{CO_2} is sufficient to explain the pH change. If so, then the disturbance is predominantly a respiratory disturbance in acid-base balance.	2. Determine the difference between the measured and predicted pH.
3. If an acute change in P_{CO_2} is insufficient to explain all of the pH change, evaluate the nature of the additional metabolic disorder. Is the metabolic disturbance consistent with the predicted compensation for a chronic respiratory change?	3. Estimate the base deficit or excess: multiply the difference between the measured and predicted pH and move the decimal point two places to the right (answer is in mEq/L).
4. If the disturbance appears primarily metabolic, evaluate the adequacy of respiratory compensation. The absence of complete respiratory compensation or of excessive respiratory compensation for a metabolic disturbance implies a secondary respiratory disturbance.	4. Calculate the anion gap to estimate the contribution of strong ions to any base deficit.
5. If a metabolic acidosis is present, ascertain the presence or absence of unmeasured anions using the anion gap or charge neutrality equations.	
6. Identify other metabolic disturbances present in the patient with an anion gap metabolic acidosis.	

suggests a combined acid-base disturbance, whereas compensation that is less than the predicted range indicates either a mixed disorder or incomplete compensation. A similar analytic approach should be used if the primary disorder is metabolic. Finally, the presence of increased amounts of unmeasured anions determines the presence of a metabolic acidosis even when [HCO_3 is normal].

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7. BRONCHOSCOPIC PROCEDURES

Beat Walder and James H. Harrell II

Since its introduction in the 1960s by Ikeda, the flexible fiberoptic bronchoscope has substantially advanced the diagnostic and therapeutic possibilities in pulmonary medicine and has replaced the rigid or open tube bronchoscope in many situations. The principal advantages of flexible bronchoscopy include (a) a more extensive view of the tracheobronchial tree; (b) ease of performance; and (c) no requirement for general anesthesia and an operating room.

Several different fiberoptic bronchoscopes are available which vary in external diameter, size of the working channel, and degree of flexion and extension of the tip. The choice depends on the specific purpose for which the instrument is to be used. A bronchoscope with an outside diameter of approximately 5.0 mm and an inside working channel diameter of 2.0 mm appears to have the widest application.

Patient preparation for elective bronchoscopy includes (a) fasting prior to the procedure to reduce the risk of aspiration (>8 hours preferable); (b) informed consent; (c) optional premedication (e.g., 0.5 mg atropine, intramuscularly, to reduce secretions); and (d) topical anesthesia (e.g., 0.45% tetracaine). In our experience, sedative drugs are rarely required during flexible bronchoscopy; if needed, midazolam can be titrated in doses of 1 to 2 mg. Routine monitoring during bronchoscopy should include continuous pulse oximetry, blood pressure, heart rate, and an electrocardiogram. All patients should receive supplemental oxygen during and after the procedure.

The flexible bronchoscope can be inserted either transnasally or transorally. We prefer the simpler transnasal approach. The oral route may be necessary with significant nasal pathology or hemostatic disorders. With the transnasal approach, flexible

bronchoscopy begins with an examination of the nasal fossa, nasopharynx, and larynx. After the anatomy and mobility of the vocal cords are evaluated, the entire circumference of the trachea is examined as the fiberoptic scope is passed through the cords. The carina is then examined for sharpness, position, and texture. All segmental bronchial orifices are inspected systematically. Careful attention is paid to their color, texture, position, relative size, and patency. The bronchial mucosa is also examined carefully to identify the presence of submucosal infiltration, degree of acute or chronic inflammation, and nature and quantity of secretions.

Specimens can be collected from the respiratory tract using a variety of sampling techniques: bronchial washing, bronchial brushing (protected or nonprotected), bronchoalveolar lavage (protected or nonprotected), endobronchial or transbronchial forceps biopsy, and endobronchial or transbronchial needle aspiration. Selected peritracheal or peribronchial lymph nodes or other lesions can also be sampled by transbronchial needle aspiration techniques. The samples obtained can be submitted for various cytologic, histologic, microbiologic, biochemical, immunologic, and molecular laboratory analyses.

Several diagnostic and therapeutic indications are seen for flexible bronchoscopy. Because of its low risk and high yield, bronchoscopy plays an important role in the evaluation of suspected lung cancer. Computed tomography (CT) of the chest is often obtained before the bronchoscopic procedure to provide additional information about the location and extent of disease, thereby identifying and localizing potential sampling sites. The diagnostic yield for directly visible lesions when a variety of sampling techniques are used is approximately 72% to 94%. Reported yields for peripheral lesions not visible endoscopically are in the range of 44% to 86%. The diagnostic yield of transbronchial procedures in peripheral nodules depends on the size of the lesion; for lesions less than 2 cm in diameter, the yield can be as low as 23% (range 23% to 58%).

Lung cancer staging is another important indication for bronchoscopy. Diagnosing cancer involvement of hilar and mediastinal lymph nodes is important for staging and treatment decisions. The yield of transbronchial needle aspiration in lung cancer evaluation depends on the absence or presence of mediastinal lymphadenopathy detected by CT scanning—approximately 10% and 50%, respectively. Bronchoscopy may also be performed before lung resection for cancer to exclude the possibility of a second, radiologically unapparent endobronchial tumor that may be present in up to 3.8% of patients.

Bronchoscopy is also used to evaluate patients after medical or surgical therapy for lung cancer. The chest radiograph is a poor indicator of recurrence or the subsequent development of second primary or metastatic cancers to which these patients are predisposed.

Hemoptysis is a common indication for bronchoscopy. The most frequent causes of hemoptysis include bronchitis, bronchiectasis, lung cancer, pneumonia, and tuberculosis. Bronchoscopy and CT are often complementary in evaluating hemoptysis, especially when lung cancer is suspected. Bronchoscopy has several potential roles in evaluating a patient with hemoptysis: (a) establish the cause; (b) determine the anatomic source of bleeding; and (c) apply therapeutic intervention(s). The diagnostic yield of bronchoscopy in hemoptysis is highest when the chest radiograph demonstrates focal findings. In this circumstance, bronchoscopy can help to determine the cause (72%) or source (10%) of bleeding in up to 82% of patients; approximately 30% of patients will prove to have a malignancy. However, with a normal or nonlocalizing chest radiograph, the detection of malignancy is much lower, averaging 6% with a range of 0 to 16%. Risk factors that increase the likelihood of cancer in bronchoscopic examination of hemoptysis include male sex, age more than 50 years, and a smoking history of more than 40 pack-years.

When the chest radiograph is normal or nonlocalizing and the bronchoscopic examination is normal, the prognosis in patients with hemoptysis is generally good. Hemoptysis resolves in most patients within 6 months. During follow-up, lung cancer is identified rarely; 1% and 6% of patients were subsequently found to have cancer at 38 and 32 months, respectively, in two studies.

Localizing the source of bleeding may be especially important with massive hemoptysis (>600 ml within 24 hours) when angiographic, surgical interventions, or both are being considered.

Potential therapeutic options that can be applied through the bronchoscope include (a) iced saline lavage; (b) topical vasoconstrictors (e.g., epinephrine); (c) endobronchial

tamponade using the bronchoscope itself or a balloon catheter (e.g., a Fogarty balloon catheter can be introduced alongside the bronchoscope, while a 200 cm pulmonary tamponade balloon can be inserted through the bronchoscope); or (d) laser photocoagulation.

The specific diagnostic yield of transbronchial lung biopsy in diffuse lung disease in nonimmunocompromised patients is approximately 38% and is very dependent on the population studied. Examples of diagnoses that can be made with bronchoscopy include sarcoidosis, lymphangitic cancer, alveolar proteinosis, and eosinophilic granuloma.

In evaluating lower respiratory tract infections, important considerations include the setting (community-acquired versus hospital-acquired), suspected organisms, and host immune competence (normal versus immunocompromised). Bronchoscopic techniques used in the diagnosis of respiratory tract infections include bronchoalveolar lavage, protected brush catheters, and, less frequently, transbronchial biopsy.

In community-acquired pneumonia, most patients are treated effectively with empiric therapy. Bronchoscopic techniques may be useful in patients who respond incompletely or transiently to empiric therapy. A similar approach has been suggested in nonventilated patients with hospital-acquired pneumonia. In ventilator-associated pneumonia, the optimal use of bronchoscopic techniques has not been well defined. Despite multiple studies, the impact of an invasive versus a noninvasive diagnostic approach on outcome measures such as mortality, cost-effectiveness, and antibiotic use has not been clearly established.

In nonimmunocompromised patients with smear-negative tuberculosis, bronchoscopy may increase the immediate diagnostic yield when smears of washings and bronchoalveolar lavage fluid are combined with stains of transbronchial biopsies. Postbronchoscopy sputum specimens may also be useful. A recent study in patients with smear-negative tuberculosis showed that induced sputum specimens had a higher immediate (smear) and ultimate (culture) yield compared with specimens obtained by flexible bronchoscopy (19% versus 12% and 74% versus 70%, respectively). In this study, however, the potential additional yield of transbronchial biopsy was not evaluated and bronchoalveolar lavage was not performed routinely.

Bronchoscopy is performed commonly to evaluate a variety of both infectious and noninfectious pulmonary complications in immunocompromised patients such as transplant recipients and those with the human immunodeficiency virus (HIV) infection. Such patients often present with nonspecific pulmonary infiltrates with many possible causes. Bronchoscopy is used commonly in these individuals, given the potentially deleterious effect of delayed diagnosis and the need for specific therapy.

Bronchoscopy can play a valuable role in selected patients with HIV. The approach to community-acquired pneumonia in this population is similar to that in the general population. Special stains of spontaneous or induced sputum specimens can diagnose *Pneumocystis carinii* pneumonia. Bronchoscopy with bronchoalveolar lavage as the primary investigative tool can increase the yield to approximately 90%. Transbronchial biopsies may increase the yield, but are rarely performed because of the excellent results obtained with bronchoalveolar lavage alone. The presentation of tuberculosis in patients with HIV varies with the CD4 count; atypical presentations are more common in patients with low CD4 counts. The yield of spontaneous and induced sputum smear examinations may be lower than in the normal host. The role of bronchoscopic diagnostic techniques appears to be similar to that in the nonimmunocompromised population. The diagnosis of Kaposi's sarcoma can be established by visualizing typical endobronchial lesions. Bronchoalveolar lavage may be very sensitive in revealing DNA evidence of human herpes virus 8, the virus that is closely associated with Kaposi's sarcoma.

In patients undergoing organ transplantation, bronchoscopic evaluation with bronchoalveolar lavage may be useful in diagnosing a variety of bacterial, mycobacterial, parasitic, and fungal infections. Cytomegalovirus infection is particularly common. The diagnosis is established by characteristic parenchymal histologic findings. In the appropriate setting, however, bronchoalveolar lavage fluid analysis with a variety of methods (cytopathology, shell vial culture, immunostaining, polymerase chain reaction) can help establish a presumptive diagnosis.

In addition to infectious complications, bone marrow and lung transplant recipients experience unique noninfectious problems in which bronchoscopy may be important in diagnosis. In bone marrow transplant recipients, the diagnosis of diffuse alveolar

hemorrhage, idiopathic pneumonia syndrome, and secondary alveolar proteinosis can be facilitated by bronchoscopy. In lung transplant recipients, bronchoscopy is useful in assessing airway complications such as anastomotic ischemia, stenosis, dehiscence, and bronchomalacia. Rejection can be diagnosed by transbronchial biopsies with a sensitivity of 72% to 94% for acute rejection and 15% to 38% for chronic rejection with a single bronchoscopic examination. Routine surveillance transbronchial biopsies to monitor for acute rejection are performed in some centers.

Bronchoscopic examination can also play an important role in intensive care and special care units as well as in anesthesia. Flexible bronchoscopy is both sensitive and specific in the diagnosis of inhalation injury, which can affect both the upper and lower respiratory tract (see Chapter 84). Inhalation injury can occur in the absence of clinical signs associated with inhalation injury (e.g., dysphonia). Furthermore, inhalation injury may or may not be associated with burns. Inspection of the upper airways may uncover edema and other mucosal abnormalities, soot, and altered bronchial secretions. Early inspection may uncover minimal or normal findings; repeated examinations may be necessary. Endotracheal intubation to protect the airway is indicated when upper airway obstruction is present or anticipated.

Tracheal or bronchial rupture is a rare complication of blunt chest trauma, usually associated with extensive trauma involving rib fractures, clavicular fractures, pneumothoraces, pneumomediastinum, and subcutaneous emphysema. Approximately 80% of tracheobronchial ruptures occur within 2.5 cm of the main carina. Diagnosis can be delayed when no communication exists between the ruptured site and the pleural space; these patients may present later with evidence of bronchial stenosis.

In anesthesia and intensive care units, flexible bronchoscopy can assist both in evaluating airways prior to, during, or after endotracheal intubation and in managing single and double lumen endotracheal tubes (insertion, positioning, exchange, and removal). Indications for bronchoscopy-guided endotracheal intubation include patients at high risk for aspiration and patients in whom cervical movement is limited or undesirable (e.g., patients with ankylosing spondylitis or cervical spine injury). In addition, bronchoscopic intubation techniques are frequently used in the context of a difficult airway, which can be defined as difficulty with mask ventilation or laryngoscopic intubation. Endotracheal tube placement can be achieved in both the awake and the anesthetized patient using either a nasal or oral approach. The nasal route generally allows for easier access to the larynx. However, factors such as the endotracheal tube size, risk of sinusitis, and bleeding risk need to be considered when choosing a nasal versus an oral approach.

In the awake patient, pharyngeal muscle tone is better maintained making visualization of the larynx easier when compared with the sedated, anesthetized, or even relaxed patient. Once the trachea has been entered with the bronchoscope, the tip of the instrument is maintained close to the main carina and a well-lubricated, premounted endotracheal tube is passed over the bronchoscope into the trachea. Proper endotracheal tube placement above the carina can be verified and the tube then secured.

For both elective and emergent intubation with the flexible bronchoscope, we prefer to use topical anesthesia alone and for the patient to be awake and sitting upright. Under these circumstances, tracheal intubation with the flexible bronchoscope is almost always successful and well tolerated. Emergent bronchoscopic intubation has a higher failure rate. Reasons for failure of bronchoscopic intubation include the inability both to visualize the larynx and to advance the endotracheal tube.

Endotracheal tube exchange can be performed with a high level of airway control by passing a bronchoscope with a premounted endotracheal tube alongside an existing endotracheal tube. The existing tube is then removed and the new tube advanced into position.

Double lumen endotracheal tubes are routinely placed with bronchoscopic control because of placement difficulties when relying on clinical judgment alone.

Upper airway inspection with an endotracheal tube in place is technically demanding. However, when extubation is contemplated in patients with known or suspected upper airway obstruction, information can be gained from examining the arytenoids, epiglottis, and vocal cords for swelling that can influence the optimal timing of extubation.

When patients are extubated with bronchoscopic assistance, the bronchoscope is passed through the endotracheal tube and initially maintained at the main carina. The endotracheal tube is pulled over the scope and the patient is observed for stridor.

The upper airway is carefully inspected while the bronchoscope is slowly withdrawn. If respiratory compromise occurs, the endotracheal tube can immediately be replaced over the bronchoscope.

Tracheostomy tube placement is often necessary for long-term ventilation. Flexible bronchoscopy plays a role in the evaluation of posttracheostomy airway complications such as granulation tissue formation (frequently located on the anterior tracheal wall superior to the tracheostomy tube), tracheal stenosis, and tracheomalacia. Tracheal stenosis related to tracheostomy can present as failure to wean from mechanical ventilatory support. Other disorders that present in a similar manner include tracheomalacia and herpetic tracheobronchitis. Bronchoscopy is essential in establishing these diagnoses. Percutaneous dilatational tracheostomy is a newer alternative to surgical tracheostomy. Monitoring tube placement with flexible bronchoscopy may improve the safety of this procedure.

Therapeutic uses of flexible bronchoscopy include removal of secretions and foreign bodies. Retained or impacted secretions are associated with atelectasis, pneumonia, lung abscess, cystic fibrosis, and middle lobe syndrome. Under elective circumstances, bronchoscopy is usually performed when conservative measures fail. When bronchoscopy becomes necessary, it is not unusual to use up to 300 ml of saline lavage to clear impacted secretions. In pulmonary alveolar proteinosis, large volume bronchoalveolar lavage (10–12 L of warm saline) through a double lumen endotracheal tube is the therapeutic procedure of choice. Foreign body removal can be attempted using a variety of special techniques and instruments (grasping forceps, baskets, and Fogarty balloons).

To perform flexible bronchoscopy safely and effectively, published guidelines should be followed. In general, flexible bronchoscopy is safe in the hands of an experienced operator. In a recent series from a university teaching hospital, major and minor complications in 4273 consecutive flexible bronchoscopic procedures occurred with a frequency of 0.5% and 0.8%, respectively. Major complications included pneumothorax (0.16%), pulmonary hemorrhage more than 50 ml (0.12%), and respiratory failure (0.2%). The frequency of major complications associated with transbronchial biopsies was 6.8% and transbronchial biopsies were involved in 48% of all major complications. No complications causing mortality were associated with bronchoscopy in this series.

Other complications associated with bronchoscopy include hypoxemia, cardiac dysrhythmias, cardiac ischemia, bronchospasm, fever, and bacteremia. Significant bleeding from bronchoscopic examinations is rare; when it occurs, it is frequently related to the performance of endobronchial or transbronchial biopsies or brushings. Bleeding risk can be assessed by elements of the patient's history (e.g., uremia, pulmonary hypertension, hepatic disease, hemorrhagic diatheses, or an immunocompromised state). Although coagulation parameters are routinely determined before bronchoscopic procedures are performed, the results of these studies may not accurately predict bleeding risk.

Transient hypoxemia is a consequence of flexible bronchoscopy; it is more common in patients with abnormal lung function or abnormal chest radiographs. Patients can experience significant hypoxemia lasting up to several hours after the procedure. To ensure adequate oxygenation during the procedure, an oxygen mask with a fenestrated diaphragm can be used through which the fiberoptic bronchoscope can be introduced. Mechanically ventilated patients are oxygenated with 100% oxygen prior to and during the procedure. Following the procedure, oxygen supplementation is gradually weaned as tolerated.

Cardiac ischemia and dysrhythmias during bronchoscopy can occur with or without a history of heart disease. Bronchoscopy has been performed safely following a recent myocardial infarction in the absence of active ischemia; however, a strict indication for the procedure is required. Bronchospasm, an unusual complication of bronchoscopy, can occur in patients with or without a history of asthma. Fever within the first 24 hours after bronchoscopy is common and has been related to the volume of liquid instilled into the airways during the procedure. Bacteremia after flexible bronchoscopy, however, is very unusual, even in patients with pneumonia. The guidelines for endocarditis prevention have recently been updated. Prophylaxis for flexible bronchoscopy with or without biopsy is optional even in patients at high risk for endocarditis. However, prophylaxis is recommended in patients at moderate or high risk for endocarditis before rigid bronchoscopy. Prophylaxis is also recommended in certain immunocompromised patients and certain patients at risk for hematogenous joint infections.

Infection control in the bronchoscopy suite is an important aspect of ensuring the safety of bronchoscopy. Both infection (transmission of an organism with disease developing in the recipient) and pseudoinfection (recovery of a tranamitted organism from a recipient without clinical disease) related to bronchoscopy have been reported. Transmission can be airborne or through contaminated instruments, including the bronchoscope itself, and ancillary equipment. General guidelines to prevent infections in the bronchoscopy suites have been published; every bronchoscopy unit should follow an infection control protocol dealing with these issues to minimize complications related to inadvertent transmission of infectious agents.

Under selected circumstances, use of the rigid bronchoscope has several advantages over the flexible bronchoscope: (a) improved airway control and ventilation; (b) larger tissue pieces and blood clots can be removed and it can be used to core out lesions; (c) it can be used to dilate stenotic airways; and (d) it allows placement of silicone stents. Rigid bronchoscopy plays a special role in managing airway obstruction. In general, the flexible bronchoscope is frequently used through the rigid bronchoscope; in fact, the rigid bronchoscope is rarely used without the flexible bronchoscope.

Malignant obstruction of the central airways is a common indication for rigid bronchoscopy. Patients undergoing the procedure commonly have inoperable malignancy, are elderly, have accompanying medical problems, or have failed other therapeutic interventions. The therapeutic goal is usually palliation, as cure is rare. Techniques available include:

1. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy
2. Dilatational therapy using the rigid bronchoscope or balloons
3. Airway stents
4. Brachytherapy
5. Photodynamic therapy

Cryotherapy and electrocautery are used occasionally.

The management of adenoidcystic carcinoma and carcinoid tumor illustrates several principles in managing airway obstruction with different bronchoscopic techniques as well as different treatment modalities (e.g., surgery, radiation therapy, chemotherapy, interventional bronchology) with palliative or curative intent. Adenoidcystic carcinoma occurs predominantly in the trachea and main stem bronchi and has a characteristic vascular appearance; this tumor frequently exhibits submucosal spread. When surgical resection is performed after debulking by the laser, the margins are frequently positive for malignancy and postoperative radiation is given. Acceptable long-term results have been achieved with this approach. Patients with unresectable tumors treated with laser and radiation therapy alone may have favorable courses. Late recurrences are seen, however. Carcinoid tumors frequently present with postobstructive pneumonia, hemoptysis, or cough. Endoscopic relief of postobstructive pneumonia may improve operability and allow more conservative resection (e.g., sleeve resection).

Benign airway stenosis is associated with a wide variety of disorders including sarcoidosis, amyloidosis, broncholithiasis, relapsing polychondritis, Wegener's granulomatosis, lung transplantation, and postintubation tracheal stenosis. Bronchoscopic techniques applied to these conditions include the Nd:YAG laser, dilatational therapy, and stents.

The Nd:YAG laser is one of the key instruments used in interventional bronchology. It provides a variety of tissue effects including coagulation, carbonization, and vaporization. Tissue penetration is approximately 4 mm. Favorable conditions for Nd:YAG laser therapy include short, endobronchial obstructing lesions with patent airways and functional lung distal to the obstruction. The best results are achieved in the large central airways (trachea, main bronchi, bronchus intermedius). Airway patency can be established in approximately 80% to 90% of patients. Besides palliation from a variety of symptoms, improvement in functional status may result. It should be emphasized that airway obstruction from extrinsic compression is a contraindication to laser therapy. Major complications related to Nd:YAG laser therapy are rare (~ 1%) and include perforations (tracheobronchial wall, blood vessels), arrhythmia, myocardial infarction, air embolism, and death. Safety and training guidelines for laser therapy have been published.

Dilatational therapy for benign airway stenosis is performed using either the rigid bronchoscope itself or with different angioplasty or valvuloplasty balloons. Typically,

sequentially larger diameter scopes or balloons are introduced into the airways. The risk of tracheobronchial tears is minimized by experience; several treatment sessions may be necessary to achieve the desired airway diameter.

The use of endobronchial stents has enhanced the armamentarium of interventional bronchologists by providing a means to maintain airway patency. Indications include (a) extrinsic compression from benign or malignant causes; (b) preparation for subsequent therapy in patients with malignancy (e.g., radiation therapy after tumor debulking by laser); (c) benign airway obstruction including tracheobronchomalacia; and (d) management of tracheoesophageal fistula. A variety of different silicone and metal stents are available. Custom-made stents can be requested from some companies. Most experience has been acquired using the Dumon type silicone stents (Hood Laboratories, Pembroke, MA). Important features include external studs that impede migration and their ease of removal. However, placement and removal require rigid bronchoscopy. Complications include migration, the development of granulation tissue at the stent margins, and impacted secretions. Stent migration in the subglottic space is a particularly difficult problem. A percutaneous suturing technique to improve retention has been described. For tracheoesophageal fistulas, successful double stenting of the trachea or left main bronchus and the esophagus has been performed.

Metal stents can be placed under bronchoscopic or fluoroscopic guidance and may not require rigid bronchoscopy. However, granulation tissue formation is common. A major disadvantage of metal stents is that they can be difficult to remove. In our view, this property makes silicone stents preferable over metal stents, especially when airway stenting may be needed transiently.

New and improved stents are continuously being developed. Comparative studies are needed to define the optimal role for the various stents.

Brachytherapy (endoluminal radiotherapy) is another treatment option for malignant airway lesions. The procedure is used mainly for palliation, although cure intent is possible for certain lesions (e.g., carcinoma *in situ*). Brachytherapy is commonly used in patients with malignant recurrences after external beam radiation. A number of different treatment regimens have been described in the literature. We prefer the high-dose rate technique using a bronchoscopically placed afterloading catheter. Dosages given at a 10-mm distance from the source (iridium 192) are either 1000 cGy (one fraction) or 660 cGy (three to five fractions at weekly intervals), depending on the indication. Response rates reported in the literature vary from 71% to 100%. Complications include necrosis, hemorrhage, and fistula formation.

Photodynamic therapy refers to treatment of tumors with sensitizers and light in the presence of oxygen. Hematoporphyrin derivatives and porfimer sodium are the sensitizers predominantly used. Following intravenous injection, they are preferentially retained by neoplastic tissue. A light source using a laser is introduced endoscopically to activate the sensitizer approximately 48 hours after injection. In the presence of oxygen, tumor necrosis is produced and normal tissue regenerates. Photodynamic therapy is approved for treating both advanced and early lung cancer. Preliminary studies suggest that photodynamic therapy allows selected patients with early lung cancer to be spared surgical resection. The major complication of this intervention is photosensitivity. The patient needs to avoid direct sun exposure for several weeks after the injection of sensitizers. In the earlier literature, complications included massive hemorrhage and fistula formation. New sensitizing drugs and treatment regimens are being studied that may result in a more widespread use of photodynamic therapy.

Outcome improvement in lung cancer would be expedited by early detection. One potential new technique for early detection is fluorescent bronchoscopy. Normal and neoplastic tissues fluoresce differently when illuminated by light of certain wavelengths. A complex imaging system coupled to a regular fiberoptic bronchoscope translates these differences into pseudoimages. A recent study in patients with known or suspected lung cancer demonstrated higher sensitivity but lower specificity in detecting moderate to severe dysplasia and carcinoma *in situ* when combining fluorescence bronchoscopy with regular white light bronchoscopy as compared with white light bronchoscopy alone.

The use of endoscopic ultrasound has been described for a variety of indications including defining tumor depth before brachytherapy and assisting in central and

peripheral transbronchial needle aspiration. One study, however, demonstrated similar diagnostic yield in transbronchial needle aspiration when ultrasound-assisted and conventional techniques were compared.

Virtual bronchoscopy is a new imaging technique simulating bronchoscopy. It represents one form of three-dimensional reconstruction of the airways made possible by recent advances in processing volumetric (helical) CT data. Further studies and developments are needed to examine the impact of these new imaging techniques on diagnostic and therapeutic bronchoscopic procedures.

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8. LUNG BIOPSY AND THORACOSCOPY

Henri G. Colt

Tissue confirmation of infectious, neoplastic, or interstitial processes responsible for focal, nodular, or diffuse pulmonary infiltrates requires sampling of lung parenchyma. Although bronchoscopy and bronchoalveolar lavage (BAL) are clearly beneficial for diagnosis of tuberculosis or *Pneumocystis carinii* pneumonia (PCP), lung biopsy is often

indicated when BAL or other less-invasive procedures do not provide diagnosis. Standard methods for lung biopsy include transbronchial biopsy (TBB), transbronchial needle aspiration (TBNA), percutaneous or transthoracic needle aspiration (TTNA), and open lung biopsy by thoracotomy (OLB).

Diagnostic strategies continually evolve, however, and are affected by interest in new technologies, concerns regarding resource allocation, and established outcome criteria. One such example is the resurgence of *thoracoscopy*. This procedure allows visualization of the lung, pleura, and mediastinum using a rigid telescope and pleural trocars through single or multiple small intercostal incisions. Thoracoscopy has been performed safely by some chest physicians and thoracic surgeons for many years, mainly for pleural biopsies and pleurodesis.

Recent improvements in instrumentation and video equipment have led to an increased use of thoracoscopic lung biopsy (TLB) and development of many video-assisted thoracic surgery techniques. TLB specimens are essentially wedge resections of lung parenchyma obtained using a disposable stapler. They are of similar size (3–6 cm) to specimens obtained during thoracotomy. Diagnostic yield is also similar, making TLB an effective alternative to formal thoracotomy for most patients. Duration of hospitalization and patient morbidity are less than after thoracotomy. Relative contraindications to TLB include a history of a bleeding diathesis (because bleeding can be difficult to control using 5- and 7-mm instruments through small pleural trocars) and a history of intolerance to general anesthesia and selective single lung ventilation (e.g., intubated and mechanically ventilated patients with profound hypoxemia and poor lung compliance). Whether TLB using reusable forceps (instead of a stapling device) provides satisfactory parenchymal sampling, lower costs, and identical low morbidity requires further investigation.

Flexible fiberoptic bronchoscopy is probably the least invasive and most cost-effective means of obtaining lung parenchyma. Bronchoscopy allows inspection of the central airways, washings, brushings, and biopsies of endobronchial lesions, if present, and lung biopsy.

Transbronchial biopsy provides samples that range from 1.5 to 2.5 mm in size. Alveolar architecture (ideally bronchioles as well) should be present for specimens to be considered adequate or representative. This is especially true in patients with interstitial lung disease and in lung transplant recipients. Diagnostic yield is probably increased when four or more specimens are obtained. In lung transplant recipients, for example, most centers advocate six to eight specimens from different lung areas because of the nonuniform nature of lung rejection. Separate specimens should be obtained for microbiology and pathology. Fluoroscopic guidance is suggested for biopsy of parenchymal nodules, masses, and localized infiltrates. In lung cancer, when lesions are greater than 3 cm in diameter, diagnostic yield is greater than 80%; with peripheral nodules less than 2 cm in diameter, yield is less than 40%. The addition of washings, brushings, BAL, and TBNA, however, can increase diagnostic yield to 60% or more.

Also, TBB is helpful in diagnosing infection in both normal and immunocompromised hosts. TBB is usually not indicated when bacterial pneumonia is suspected but is extremely helpful for the diagnosis of smear-negative tuberculosis, PCP, and fungal or viral infections (biopsy specimens confirm tissue invasion with organisms), especially when BAL is negative. With diffuse bilateral infiltrates on chest radiographs, specimens are obtained from multiple segments of one lung only because of the risk of complications.

Disease processes with peribronchial predominance (e.g., sarcoidosis, lymphoma, or lymphangitic spread of cancer) are more likely to be diagnosed by TBB than are other diffuse processes. Other diseases commonly diagnosed by TBB, however, include alveolar proteinosis, pulmonary hemosiderosis, Goodpasture's syndrome, and eosinophilic granuloma. Less commonly diagnosed are Kaposi's sarcoma, lymphomatoid granulomatosis, hypersensitivity pneumonitis, Wegener's granulomatosis, bronchiolitis obliterans, and other specific causes of alveolitis or interstitial pulmonary fibrosis. Possible reasons for a less than satisfactory diagnostic yield in these instances are small specimen size, loss of tissue architecture, and collapse or crushing of biopsy samples by forceps that makes pattern recognition difficult for the pathologist. A diagnosis of inflammation or fibrosis should probably be considered nonspecific, prompting a more aggressive diagnostic approach, if clinically indicated.

Transbronchial needle aspiration is performed during bronchoscopy, principally for diagnosis and staging of lung cancer. Diagnostic yield is a function of instrumentation, operator experience, technique, perseverance, and lesion accessibility. TBNA will provide samples from mediastinal lymph nodes or tumors adjacent to the major airways. Depending on the needle, specimens are obtained for cytology or histology. Needles vary in size from 18 gauge to smaller 22-gauge and are usually retractable into a protective sheath designed to prevent laceration of the bronchoscope during insertion and withdrawal. Some needles have inner stylets to improve rigidity. The addition of fluoroscopically guided TBNA to TBB may improve diagnostic yield in peripheral lesions. TBNA also enables sampling of mediastinal lymph nodes, especially in the paratracheal (group 4), subcarinal (group 7), and perihilar regions (group 10). A thorough knowledge of thoracic and mediastinal anatomy is essential. Computed tomography (CT) scans of the chest are helpful to guide bronchoscopic sampling. Histology specimens are less likely to yield false-positive results than cytology specimens. Positive aspiration, however, in patients without evidence of nodal enlargement on imaging studies should be interpreted with caution. Decisions regarding unresectability should be based on firm evidence of mediastinal extension. Mediastinoscopy or mediastinotomy may be indicated, and a multidisciplinary approach to cancer therapy is advocated.

Complications of TBB and TBNA include pneumothorax, which can occur in up to 3% of patients, and bleeding. Risk of pneumothorax probably increases with forceps size, number of specimens, and whether patients have hyperinflated lung or cystic disease such as bullous emphysema, cystic fibrosis, or acquired immune deficiency syndrome (AIDS) with a history of PCP or pneumothorax. Fluoroscopic guidance increases diagnostic yield and decreases incidence of pneumothorax. Scant, transient hemoptysis often occurs after TBB and is of no consequence. Frank bleeding (>50 ml) can occur, however, especially if pulmonary or bronchial arteries are inadvertently biopsied, or in patients with cavitating lesions. To avoid complications, take a complete history, perform a thorough physical examination, and obtain a coagulation profile. Patients with pulmonary hypertension, uremia, or a known coagulopathy and individuals taking anticoagulants are at high risk.

Procedures should be performed by trained personnel in a bronchoscopy suite fully equipped for emergency resuscitation. Bronchoscopists should be familiar with laryngoscopic or bronchoscopic endotracheal intubation techniques, chest tube insertion, and endoscopic techniques used to stop bleeding.

Transthoracic needle aspiration is especially helpful for lesions inaccessible to bronchoscopy (e.g., central masses, peripheral lesions abutting the pleura or chest wall) or when bronchoscopy is nondiagnostic. TTNA using biplane fluoroscopic guidance is less costly and less time-consuming than CT-guided TTNA, which is usually reserved for lesions that cannot be well visualized fluoroscopically or for lesions adjacent to vascular structures. Ultrasound guidance is promising but can be used only in lesions abutting the pleural surface.

Large-bore cutting needles have been used for TTNA but result in a greater number of complications, including potentially fatal air embolism. With smaller needles (18–22 gauge), complications are less frequent and sensitivity for diagnosis of malignancy in peripheral lesions is greater than 85%. The specific yield in benign lesions, however, ranges from 12% to 68%. A nondiagnostic aspirate, therefore, cannot exclude malignancy. A false-negative TTNA finding usually results from inadequate sampling or tissue necrosis. For these reasons, multiple samples from the lesion's center and periphery are advocated. Specimens should always be processed for cytology and microbiology, including Gram's stain, fungal stains, and culture, because TTNA is particularly helpful in diagnosing granulomatous infection.

Complications of TTNA include pneumothorax and, occasionally, bleeding. Malignant seeding of the needle tract, although described, is extremely infrequent. Pneumothorax can occur in 5% to 60% of instances, but chest tubes are necessary in less than 20% of cases. Pneumothoraces have been related to extent of operator experience, needle size, number of passes, depth of the lesion from the skin, and presence of obstructive lung disease. Most occur immediately or within 1 hour after the procedure, so chest radiographs should be obtained after TTNA.

Open lung biopsy is the standard to which all lung biopsy techniques are compared. Diagnostic yield can vary, however, depending on whether the radiographically most

involved lobe is sampled. Usually, at least two separate specimens are obtained. CT assessment of abnormalities helps to determine areas that should be sampled. Although the indications for surgical lung biopsies remain controversial, it appears that many healthcare providers have become more inclined to proceed to lung biopsy since the introduction of thoracoscopic wedge resections. In the presence of diffuse infiltrates and suspected infection, particularly in patients with AIDS or malignancy, investigators have suggested a limited role for OLB. In selected patient populations, however, such as when vasculitis, active interstitial pneumonitis, bronchiolitis, or infectious (aspergillosis, cytomegalovirus, or other viral pneumonias) lung disease are suspected, lung biopsy results, even when negative, help guide therapy. On occasion, specific causes altering medical therapy may not be identified and biopsy results may not effect outcome. Most agree that when less invasive procedures are nondiagnostic, appropriate timing of OLB or TLB requires careful consideration of clinical status, potential causes, therapeutic options, a planned management strategy based on biopsy findings, and an overall assessment of outcome probabilities and prognosis.

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9. MEDIASTINAL EXPLORATION

John E. Barkley

Surgical exploration of the mediastinum is useful for staging bronchogenic carcinoma before thoracotomy and for evaluating other causes of mediastinal lymphadenopathy (e.g., lymphoma, sarcoidosis, and tuberculosis). Although the terms mediastinoscopy, mediastinotomy, and extended cervical mediastinoscopy are often used interchangeably, they are quite different procedures with different indications and risks.

Mediastinoscopy was first introduced by Carlens in 1959 as a staging technique to assess the operability of bronchogenic carcinoma. The procedure is performed by making a 3-cm transverse incision between the thyroid cartilage and the suprasternal notch. The dissection is carried down through the pretracheal fascia, and a plane is developed between the trachea and the innominate artery, aorta, and pulmonary artery by blunt dissection. The mediastinoscope, similar in design to a Jackson straight laryngoscope, is introduced into the incision, using the anterior tracheal and bronchial cartilaginous rings as reference points. Lymph nodes accessible at mediastinoscopy include the right and left upper paratracheal American Joint Committee on Cancer (AJCC) stations 2R and 2L; the right and left lower paratracheal, AJCC stations 4R and 4L; and subcarinal, AJCC station 7, nodes. Tracheobronchial angle nodes, AJCC stations 10R and 10L, are within the pleural reflection; they are now designated as N1 (hilar) and, therefore, cannot be biopsied without creating a pneumothorax. The subaortic, AJCC station 5; paraaortic, AJCC station 6; paraesophageal, AJCC station 8; and inferior pulmonary ligament, AJCC station 9, nodes cannot be biopsied via cervical mediastinoscopy. In experienced hands, reported complications are infrequent, occurring in approximately 4% of cases. The most frequent complication is right-sided pneumothorax, resulting from inadvertent transmediastinal pleural biopsy of the lung; other reported complications include hemorrhage, recurrent laryngeal nerve damage, injuries to the trachea and

esophagus, and wound infections. Mortality is exceedingly rare; no deaths were reported in two series that analyzed results from 2259 procedures.

Anterior (parasternal) mediastinotomy was originally introduced by McNeill and Chamberlain in 1966 as an alternative to cervical mediastinoscopy. It is currently used to evaluate anterior mediastinal lymph nodes in cases of left upper lobe carcinoma and as a means to perform a biopsy of anterior mediastinal masses. Nodal groups unreachable by traditional cervical mediastinoscopy—aortopulmonary nodes and anterior mediastinal nodes, AJCC stations 5 and 6—are approachable by this technique.

Many modifications of McNeill and Chamberlain's initial procedure have been reported. An incision can be made either over the second costal cartilage, which is then excised, or in an intercostal location without any cartilage excision. An intrapleural or extrapleural approach can be used. Following blunt dissection and digital palpation, a mediastinoscope is then inserted to identify and enable biopsy of lymph nodes in the involved chains. Although experience with anterior mediastinotomy is considerably less than that with cervical mediastinoscopy, the complication rate appears similar.

Ginsberg and colleagues have reported results with extended cervical mediastinoscopy, which allows access to superior and anterior mediastinal lymph nodes in a single procedure. Following traditional cervical mediastinoscopy, the pretracheal fascia is broken down digitally and the mediastinoscope is passed over the aortic arch, between the left carotid and innominate arteries and posterior to the left innominate vein, to sample subaortic and para-aortic lymph nodes. A single superficial wound infection was the only complication in a series of 100 consecutive cases. More experience with this procedure must be obtained before its widespread use because of the potential for injury to so many major vascular structures.

Transbronchial needle aspiration has proved to be a valuable and less-invasive means of evaluating the status of mediastinal lymph nodes before thoracotomy. However, its exact role in staging bronchogenic carcinoma needs to be defined. False-positive findings of aspirates, although rare, have been reported. Additionally, increasing evidence indicates that a number of variables can influence the resectability rate of bronchogenic carcinoma. These include the site and extent of mediastinal extension and whether this extension is intranodal or extranodal in nature—data that cannot be obtained by a blind transbronchial approach. Transbronchial needle aspiration can provide valuable histologic information in patients with extensive disease in whom resection is considered unlikely on the basis of clinical or computed tomography (CT) scan criteria. Whether a finding of normal-sized lymph nodes on CT scan and a positive aspirate determine that disease is unresectable remains to be defined.

Exactly which patients with bronchogenic carcinoma should undergo or, more precisely, not undergo mediastinal lymph node biopsy before thoracotomy remains controversial. No patient should be denied the opportunity of surgical cure based on imaging techniques alone. Neither should a patient undergo the risk of a needless thoracotomy if a less-invasive technique will establish unresectability. Whereas CT scanning of the chest is considered a standard part of the preoperative assessment of patients with bronchogenic carcinoma, the sensitivity and specificity are poor at approximately 65%. Positron emission tomography (PET) has better sensitivity and specificity for detecting lymph node metastases and can help direct the surgeon toward particular lymph node groups that show increased activity on PET scanning. The roles of CT scanning, PET, bronchoscopy, mediastinoscopy, and mediastinotomy will continue to evolve with advancements in molecular biology, immunohistochemistry, prognostication, and therapy of bronchogenic carcinoma.

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10. PREOPERATIVE PULMONARY EVALUATION

Jack L. Clausen

Preoperative pulmonary evaluation (PPE) serves to identify the individual who is at significant risk of postoperative morbidity and mortality from either pulmonary complications or resection of lung tissue *per se*. Potential complications include postoperative atelectasis, pneumonia, and ventilatory failure, as well as long-term respiratory insufficiency induced by pulmonary resection. Ideally, PPE allows optimization of preoperative and postoperative regimens to prevent problems and enables exclusion from surgery of patients with unacceptable risks.

Advances in surgical procedures and improvements in perioperative respiratory management have had a significant impact on the conclusions derived from earlier data regarding less advanced clinical conditions. Advances in patient care have prompted the periodic reassessment of PPE benefits, the criteria used to preclude surgery, and the predictive indicators of postoperative complications. Studies in institutions with highly specialized teams for perioperative management may not be relevant to similar patients undergoing surgery in small rural hospitals. Consequently, guidelines regarding preoperative evaluation of patients are often controversial. Randomized controlled trials might clarify the value of PPE but are rare and seldom feasible. Prospective studies regarding the usefulness of specific risk factors for predicting morbidity and mortality are supplanting older retrospective data.

The prevalence of pulmonary complications is influenced by the type and site of surgery, the degree of preoperative pulmonary dysfunction, and the presence of other diseases. Anesthesia and surgical procedures can lead to pulmonary complications via several mechanisms. During general anesthesia, functional residual capacity is usually decreased and periodic deep breaths (sighs) and the ability to cough are abolished. Postoperatively, blunting of coughs and deep inspirations by pain and treatment with narcotics and analgesics can contribute to postoperative atelectasis, impaired clearance of airway secretions, respiratory infections, and in some patients, ventilatory insufficiency. The site of the surgery affects the incidence of complications: thoracotomy and upper abdominal surgery are associated with a threefold greater risk for pulmonary complications compared with extremity surgery. Thoracotomy with resection of lung tissue not only predisposes the patient to postoperative pulmonary complications (PPC) but also can result in chronic respiratory insufficiency. Routine preoperative chest radiographs generally are not indicated for patients aged less than 60 years and without risk factors indicative of lung disease; they should be done selectively in patients with one or two risk factors. For patients with three or more risk factors by clinical history, a preoperative chest radiograph should be routine. A chest radiograph is usually indicated for patients older than 60 years, even for those with no risk factors. Studies assessing benefits from preoperative chest films in terms of improved outcome are not available.

Aside from the quality of perioperative care, the most important predictor of PPC is the presence of abnormal pulmonary function. Most patients who develop PPC (>90%) have abnormal lung function. The first step in avoiding PPC is a careful history and physical examination. Patients with a history of cigarette smoking, unexplained dyspnea, asthma, chronic obstructive pulmonary disease, or other chronic respiratory illness are at greater risk and should undergo preoperative pulmonary function testing (PFT). The minimal evaluation includes simple spirometry and an arterial blood gas (ABG) analysis. The most useful spirometric parameters are the forced vital capacity (FVC), forced expiratory volume during the first second of the FVC maneuver (FEV_1), and the FEV_1:FVC ratio. The presence of PFT abnormalities should prompt efforts to mitigate the risk of PPC by appropriate preoperative management aimed at optimizing lung function (e.g., smoking cessation, bronchodilators, and antibiotics). The degree of PFT dysfunction should also guide (a) the selection of anesthetic technique (spinal or epidural versus general anesthesia); (b) the choice of surgical procedure if alternatives exist (less invasive or shorter); and (c) the type of postoperative monitor-

ing and pulmonary management. Few absolute criteria of pulmonary dysfunction preclude surgery that is otherwise indicated, given the advances in surgical techniques and postoperative management.

Although a growing number of studies have concluded that obesity *per se* is not a risk factor for pulmonary complications after surgery, other studies have concluded it is a significant (and independent) risk factor. Studies have not always controlled well for comorbidity, and it may be that even massive obesity increases the risk of postoperative complications only if other pulmonary risk factors are present.

Patients with obstructive sleep apnea may have surges of catecholamines and cardiac arrhythmias during apneas that place them at risk for sudden death after extubation. Such patients should be carefully monitored during sleep or treated with continuous positive airway pressure (CPAP) when sleeping or during sedation. Patients with a history suggestive of sleep apnea should undergo preoperative sleep testing. If this is not an option, they should be carefully monitored after extubation and assessed for empirical deployment of CPAP. Such patients also require more careful monitoring during minor procedures in which sedating agents are used.

Patients with abnormal pulmonary function tests, particularly a decreased FEV_1:FVC ratio, have a 20% to 40% chance of developing PPC. In many patients, this risk can be significantly reduced ($\geq$ 50%) by aggressive preoperative preparation, including use of bronchodilators, hydration, chest physiotherapy, and, when appropriate, antibiotic therapy. Although preoperative cessation of cigarette smoking is a widespread recommendation, it is usually difficult to achieve for the period of time considered necessary to gain benefits (~ 8 weeks). If pulmonary complications do occur, they are less severe in patients who undergo appropriate pulmonary care preoperatively. Prophylactic use of intermittent positive pressure breathing treatments has not proved helpful in preventing postoperative complications. Many studies have indicated that elevations of arterial $Paco_2$ correlate with higher postoperative complication rates. Recent studies have not confirmed these observations, however, perhaps reflecting improvements in perioperative management of patients with significant lung dysfunction. Although an elevated preoperative $Paco_2$ may not preclude surgery, it should prompt a search of potential causes and efforts to improve lung function. If the $Paco_2$ remains above the upper limits of normal (47 mmHg) or the vital capacity less than 1 L after aggressive preoperative therapy, a significantly increased risk exists for PPC. It is preferable to classify patients with function outside these limits as *high risk* (as opposed to *prohibitive risk*) for whom surgery should be considered only after carefully balancing the benefits of operation versus postoperative risks.

Death in the operating room is now much less common than in the postoperative period. When pulmonary resection is contemplated, consideration must be given to the patient's long-term functional status after resection in addition to consideration of the predicted perioperative morbidity and mortality. Long-term functional status is affected by two major variables: (a) the extent of resection contemplated and (b) the functional contribution of the lung zones to be resected versus that of the lung zones that will remain. Because of the occasional need to perform more extensive resection at the time of surgery than initially planned, predictions should be made for the spectrum of surgical procedures that might be required.

The first step in predicting postresection lung function is to adequately treat any reversible components before assessment. This step may transform a marginal candidate into one with an acceptable risk. The second step is to review the results of standard spirometry and ABG values obtained at rest. If these values are satisfactory, rarely is a need seen to proceed. If the values indicate significant lung dysfunction, however, it is important to recognize that standard pulmonary function tests provide information about the composite function of all lung zones and not the relative contributions of specific lung regions. If the FEV_1 is less than 1.6 L or less than 40% of predicted, or an ABG demonstrates hypercapnia or substantial hypoxemia, regional lung function should be assessed. Formerly, bronchospirometry and lateral position tests were used for this purpose. These procedures now have been replaced, except in rare instances, by ventilation and perfusion lung scans. Ventilation (V) and perfusion (Q) scanning allows assessment of the distribution of blood flow, ventilation, and $\dot{V}/\dot{Q}$ matching in those zones that can be resected versus those remaining. For example, if a lung region to be resected has essentially no perfusion, that resection will

not have a significant impact on overall function. On the other hand, it may be discovered that the regions to be resected carry the major share of both perfusion and ventilation, in which case resection is contraindicated. Thus, in the marginal candidate for resection, V and Q studies can affect significantly the final decision. In many cases, perfusion scans alone suffice for this purpose, obviating the need for ventilation scans. V/Q scans can also be used to predict postoperative pulmonary function as quantitative indices for resectability [e.g., FEV_1, (diffusing capacity for carbon monoxide (DLCO), or maximum oxygen consumption ($\dot{V}O_2max$)].

In those uncommon cases in which extensive pulmonary vascular disease is suspected, or in marginal cases, unilateral pulmonary occlusion may be indicated as a guide to the hemodynamic status after resection. A precipitous rise in pulmonary artery pressure suggests significant pulmonary vascular disease and a poor outcome after resection. The observation that measurements of pulmonary vascular resistance during exercise may be a useful predictor of postoperative mortality is provocative, but awaits confirmation from prospective studies before this invasive approach can be recommended widely. Less invasive tests of exercise function, such as measurements of maximal oxygen consumption or the ability to complete defined amounts of exercise (e.g., 6-minute walks, stair-climbing), may prove to be useful for the evaluation of the patient with pulmonary hypertension, but their exact role awaits additional prospective studies.

Advances in surgical techniques and improvements in the quality of routine postoperative respiratory care have led to the conclusion that routine pulmonary testing of all patients is no longer indicated. Indications for screening spirometry and an ABG have included all patients with a history or signs of pulmonary disease, cigarette smoking, obesity, or aged more than 60 years and all patients undergoing thoracotomy. The final decision for surgery, whether for pulmonary resection or for nonthoracic procedures, also must take into account several other factors: (a) the patient's overall condition (particularly the presence of comorbidities such as coronary artery disease and the patient's mental status); (b) the availability and relative risk-to-benefit ratio of alternative (nonsurgical) treatment options; and (c) the expertise of those who will manage the patient during and after surgery. The importance of the latter cannot be overemphasized. With meticulous care, few patients cannot be operated on successfully in the face of an overwhelming indication for surgery. Even patients with moderate pulmonary compromise can have significant morbidity and mortality if special care is not taken in the preoperative, intraoperative, and postoperative periods. No evaluation, however sophisticated, can substitute for optimal care in these patients.

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11. RIGHT HEART CATHETERIZATION AND MONITORING OF ARTERIAL PRESSURE

Robert M. Jasmer

The flow-directed, balloon-tipped (Swan-Ganz) pulmonary arterial catheter can provide invaluable hemodynamic data in patients with acute and chronic pulmonary disease. The standard multilumen device allows measurement of pressures and flow, sampling of *mixed* venous blood, and delivery of diagnostic and therapeutic agents

directly into the pulmonary vasculature. Right heart catheterization does have certain risks. Although these risks can be minimized with the proper technique, the primary indication for use of the catheter is the need for specific data not available by less invasive approaches.

The major indications for pulmonary artery catheterization among patients with pulmonary disease include (a) distinguishing between cardiogenic and noncardiogenic pulmonary edema (acute respiratory distress syndrome; (b) the diagnosis, or exclusion, of left ventricular failure among patients with chronic obstructive or restrictive pulmonary diseases who develop increasing dyspnea; (c) the detection and quantification of pulmonary hypertension; (d) evaluation of the response to pulmonary vasodilating agents; and (e) assistance in the fluid and ventilator management of patients with respiratory failure or following pulmonary surgery. In each of these situations, ample data have established that less invasive techniques fail to provide adequate information to manage patients correctly. For example, central venous pressure (CVP) monitoring often is relied on for assessing left ventricular end-diastolic pressure, yet it can provide spurious information regarding pressures beyond the pulmonary valve. In patients with severe left ventricular failure or pulmonary hypertension, the CVP may be normal or increased. Increasing the CVP does not provide the cause (i.e., right ventricular failure alone or secondary to left atrial or left ventricular dysfunction).

When a branch of the pulmonary artery is momentarily occluded by the balloon, blood flow in it and in the downstream pulmonary veins ceases. In this no-flow situation, the pressure recorded by the catheter tip (the pulmonary artery occlusion pressure [PAOP]) is transmitted through the pulmonary veins from the left atrium. Therefore, under normal circumstances, the PAOP reflects left atrial pressure, which is the same as left ventricular end-diastolic pressure when the mitral valve is open. With obstruction or constriction of the pulmonary veins (e.g., venous thrombosis, mediastinitis, left atrial myxoma, or thrombi), the PAOP will exceed left atrial pressure. The PAOP also fails to reflect left ventricular end-diastolic pressure accurately in the presence of mitral valve disease, especially mitral stenosis, as well as in conditions of disturbances of left ventricular compliance. Finally, PAOP may not accurately reflect left ventricular hemodynamics if alveolar pressure exceeds pulmonary artery pressure. This condition can occur during mechanical ventilation or, spontaneously, if the pulmonary artery catheter is placed into a *zone* of the lung (1 or 2) in which the alveolar pressure exceeds the arterial pressure. In such situations, accuracy can be ensured by placing the catheter into *zone 3*, briefly interrupting mechanical ventilation, or by measuring only during end expiration. Cardiac output measurements by the thermodilution method have been shown to be as accurate as those obtained by other methods (Fick, indicator dilution) as long as a careful technique is used.

Right heart catheterization should be performed using sterile surgical techniques. The catheter balloon should be tested before insertion because up to 3% can be defective. Percutaneous insertion, without fluoroscopy, is possible in almost all patients. The subclavian and internal jugular veins are the most common insertion sites. Under continuous pressure monitoring, the catheter is advanced until the tip enters the thorax. An intrathoracic position is signaled by the appearance of respiratory fluctuations in the pressure tracing, at which time the balloon is inflated and the catheter advanced (Fig. 11.1). Once the right ventricular (RV) pressure configuration is noted, the pulmonary artery should be reached with no more than 15 cm of additional catheter advancement. If difficulties arise in reaching the pulmonary artery, an injection of 10 to 20 ml of iced saline via the distal port may stiffen the catheter and facilitate advancement.

Once the pulmonary arterial pressure tracing is obtained, the catheter is advanced until it wedges (Fig. 11.1). The balloon is deflated and the catheter advanced until a wedge tracing is again seen. After inflation of the balloon with between 0.6 and 0.8 ml of air, the catheter is slowly withdrawn until a wedge tracing is obtained. With this technique, excess catheter is not left in the right ventricle. A chest radiograph should be obtained to document catheter position.

Pressure recording systems should be physically and electronically calibrated at least once daily. Pressures must be measured with the patient in the same position relative to the transducer. Usually the transducer is placed 4 cm posterior to the sternomanubrial joint or 10 cm from the top of the bed.

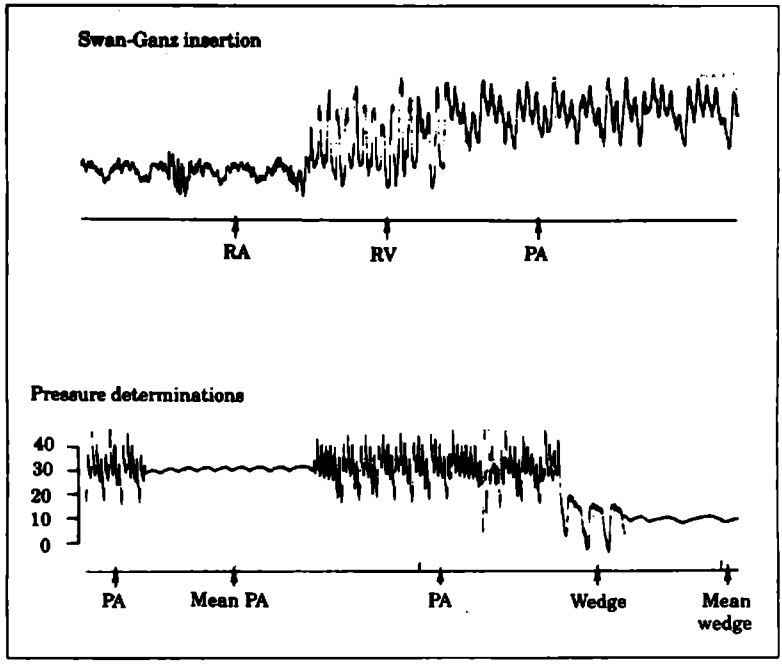

FIG. 11.1. Typical pressure configurations observed as the pulmonary artery catheter (Swan-Ganz) passes through the right atrium (RA), right ventricle (RV), pulmonary artery (PA), and into the pulmonary wedge position. (Courtesy of Stuart J. Menn, M.D., Veterans Administration Hospital, San Diego, California.)

Complications of Swan-Ganz catheterization should be rare if appropriate precautions are taken. Premature ventricular contractions are the most frequent complications; they usually occur when the catheter is passing through the right ventricle. If they occur, the catheter should be advanced or removed. Close electrocardiographic monitoring during advancement through the right ventricle is essential. Patients with a left bundle branch block can develop complete heart block if the right bundle branch is transiently traumatized. For such patients, the operator should be skilled in pacemaker placement, or a cardiologist must be readily available before right heart catheterization is attempted.

Pulmonary infarction due to pulmonary artery catheterization can be caused by obstructing pulmonary blood flow for a significant length of time. It can be avoided by (a) wedging the catheter as infrequently and as transiently as necessary; (b) having only designated, trained personnel inflate and deflate the balloon; and (c) continuous monitoring of pulmonary artery pressure for evidence of damping or difficulty in achieving a wedge tracing after normal balloon inflation. If the balloon requires 0.5 ml of air or less for *wedging*, it is too distal and should be withdrawn to a position where 0.8 to 1.0 ml of air produces the wedge tracing. Rupture of small vessels can be avoided by gradual inflation of the balloon and stopping inflation as soon as the wedge tracing is seen.

The most devastating complication is pulmonary artery rupture, which has a high mortality. Pulmonary hypertension and anticoagulation are the major risk factors, but

the factors associated with pulmonary artery infarction are also associated with rupture. A contained perforation should be considered in any patient who develops hemoptysis with a pulmonary arterial catheter in place. A chest computed tomography scan can be diagnostic.

Local infection can occur at the catheter insert site. Its incidence can be reduced by attention to strict asepsis during and after catheter insertion, by not advancing the catheter distally following initial placement, and by changing catheters after they have been in place for 72 to 96 hours. Venous thrombosis along the catheter path also is a common complication, occurring in up to two thirds of patients with internal jugular insertion sites. The widespread availability of heparin-bonded catheters has reduced this incidence. However, such catheters should not be used in patients with existing or prior heparin-associated thrombocytopenia.

With attention to these conceptual and technical considerations, right heart catheterization can provide invaluable information regarding the hemodynamic status of patients with acute and chronic pulmonary disorders.

Monitoring of Arterial Pressure

Insertion of an intraarterial catheter for continuous monitoring of blood pressure is indicated for patients with hemodynamic instability, those in whom vasoactive medications are administered, and in patients with respiratory failure who require frequent blood gas analysis. The most common site for an arterial line is the radial artery. Before insertion into the radial artery, an Allen test should be performed to confirm adequate collateral flow via the ulnar artery. Other sites for arterial cannulation include the ulnar, brachial, femoral, and dorsalis pedis arteries. The term *over-damping* has been applied to inaccurate recording of pressure that results in a waveform that is blunted. Air bubbles in the pressure tubing are the most common cause. The result is that the systolic will appear lower and the diastolic higher than the actual pressure.

Potential complications of arterial catheters include local hemorrhage, infection, and thrombosis. Hemorrhage can usually be controlled with local compression. Risk factors for infection include placement by surgical cut-down, local inflammation, and a longer duration of cannulation. Clinically significant arterial thrombosis occurs in less than 1%. Risk factors for ischemia include a large bore cannula, hypotension, severe peripheral vascular disease, and the use of vasoactive medications.

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II. SPECIAL PROBLEMS

12. PLEURAL EFFUSION

Henri G. Colt

A few milliliters of pleural fluid is normally present within the pleural space, serving as a lubricating film between the visceral and parietal pleural surfaces. In normal individuals, thoracentesis generally yields less than 1 ml of fluid, although quantities of 3 to 20 ml have been obtained in as many as 10% of healthy individuals in some series. Normally, the protein content of pleural fluid is below 1.5 g/dl; the protein electrophoretic pattern is qualitatively similar to plasma, although the content of albumin is slightly higher and that of fibrinogen slightly lower.

The volume and composition of pleural fluid are maintained virtually constant in healthy individuals by an intricate balance of hydrostatic and oncotic pressures and by the relative permeabilities of the pleural capillaries and lymphatics. Systemic arteries supply the parietal pleura, whereas the visceral pleura is supplied by the bronchial arterial circulation. Fluid and protein exchange in the pleural space is almost exclusively achieved via the parietal pleura.

Pleural effusion is defined as the abnormal accumulation of fluid within the pleural space. It may be caused by either excess fluid production or decreased absorption; in some conditions, both mechanisms may be operative. Effusions are a common manifestation of both systemic and intrathoracic diseases. The factors that condition whether pleural fluid accumulates include (a) oncotic pressure in the pleural fluid, the pleural microcirculation, and lymphatics; (b) the permeability of the pleural microcirculation; and (c) the pressures in the systemic veins and the pulmonary veins. These factors are embodied in Starling's equation (Fig. 12.1). However, this balance can also be altered, favoring fluid accumulation, by any process that obstructs lymphatic drainage. Also, peritoneal fluid can gain access to the pleural space via both diaphragmatic defects and transdiaphragmatic lymphatics. Thus, under a wide variety of circumstances pleural fluid exchange can be compromised, leading to the development of a pleural effusion.

The most common cause of a pleural effusion is congestive heart failure with elevation of the pulmonary venous pressure. Whether elevation of systemic venous pressure alone (*pure right heart failure*) prompts pleural effusions remains controversial, but elevations of both venous pressures appear to result in larger effusions.

Increased negativity of pressure in the pleural space also encourages fluid accumulation, which can occur in patients with atelectasis. Although decreased plasma oncotic pressure favors pleural fluid accumulation, it is unlikely this mechanism acts alone, because effusions are rare in congenitally hypoalbuminemic individuals.

Increased capillary permeability caused by local inflammation, circulating toxins, or vasoactive substances also plays a role in fluid accumulation associated with collagen-vascular diseases, pancreatitis, pulmonary emboli, and pneumonitis. An increase in pleural oncotic pressure as a consequence of (a) enhanced capillary protein leak, (b) protein exudation from local pleural inflammation or tumor, or (c) defective lymphatic resorption contributes to some effusions. As pleural space oncotic pressure approaches that of plasma (32 cm H_2O), fluid resorption is impaired.

Simple transfer of ascitic fluid across diaphragmatic defects has been invoked as a mechanism for pleural effusions accompanying ascites, as in cirrhosis and Meig's syndrome. A similar mechanism has been proposed for fluid accumulation in pancreatitis or subdiaphragmatic abscess, although enhanced transdiaphragmatic lymph flow can also play a role.

Patients with pleural effusions can have dullness to percussion, diminished breath sounds, and reduced tactile and vocal fremitus over the involved hemithorax on physical examination. Altering the patient's position will occasionally *shift* these physical findings to dependent regions of the hemithorax. Large effusions (>1500 ml) are frequently associated with an appreciable inspiratory lag, bulging intercostal margins,

$\dot{Q}_f = K_f[(P_{MV} - P_{PMV}) - \sigma(\pi_{MV} - \pi_{PMV})]$

where $\dot{Q}_f$ is the net transvascular flow;

K_f is the fluid filtration coefficient, reflecting the permeability of the membrane to fluid;

σ is the apparent reflection coefficient, which takes into account the effect of protein permeability in determining the effective transvascular osmotic pressure difference;

P_{MV} and P_{PMV} are the hydrostatic pressures of the microvascular and perimicrovascular spaces; and

π_{MV} and π_{PMV} are the microvascular and perimicrovascular protein osmotic pressures.

FIG. 12.1. Starling's equation.

contralateral mediastinal shift, or atelectasis (e.g., egophony, bronchial breath sounds). A search should always be made for nonthoracic signs suggestive of the cause of fluid accumulation (e.g., pedal edema, distended neck veins, and an S_3 gallop suggesting congestive heart failure).

Often, the chest roentgenogram is the only clue to the presence of an effusion, and may suggest its cause (e.g., cardiomegaly and redistribution of pulmonary veins in heart failure; lung or pleural-based masses, atelectasis, rib erosions signifying a metastatic carcinoma; or an elevated hemidiaphragm suggesting subdiaphragmatic abscess, volume loss, or bronchial obstruction). At least 150 ml of fluid is required to detect an effusion on a standard posteroanterior and lateral chest roentgenogram. Classically, fluid initially collects between the anteroinferior lung surface and the diaphragm. It then obliterates the costophrenic angle on the frontal view or creates a triangular density that obscures the ipsilateral diaphragm and posterior costophrenic sulcus on a lateral film. Further accumulation obliterates the hemidiaphragm and opacifies the hemithorax with an upward concavity that extends higher laterally than medially. On the lateral view, pleural fluid ascends obliquely along the posterior chest wall. Significantly smaller quantities of pleural fluid are detectable on lateral decubitus views, but these are often not necessary because fluid (both loculated and free flowing) can be easily detected by pleural ultrasonography before thoracentesis. On lateral decubitus films, fluid layers along the dependent chest wall. On the opposite decubitus view fluid shift allows examination of underlying parenchyma. As mentioned, a very large effusion should cause a contralateral mediastinal shift. When this shift does not occur, parenchymal collapse or mediastinal fixation, often from a tumor, is suggested.

When underlying parenchymal abnormalities or adhesions between pleural layers exist, atypical patterns of fluid accumulation result. A subpulmonic effusion can harbor more than 1000 ml of fluid and appear only as an elevated hemidiaphragm. The *diaphragmatic* contour is often more horizontal than usual, with a steep angulation laterally, creating a shallow costophrenic angle. A lateral decubitus film may layer the fluid and reveal the true diaphragmatic shadow. When pleural fluid becomes loculated (or entrapped) within an interlobar fissure, it can create the appearance of an elliptic opacity, or *pseudotumor*, on the posteroanterior film and a spindle-shaped opacity tapering into fissure lines on the lateral film. For unknown reasons, this appearance is especially common with congestive heart failure and resolves as hemodynamics improve. Fluid that is loculated laterally can result in a smooth, contoured semicircular opacity abutting a pleural surface, which can simulate a mass lesion on a posteroanterior film. Loculations are frequently seen in patients with evolving parapneumonic effusions or empyema, after thoracic surgery, or following pleurodesis.

The major exercise that must be used for all patients with an effusion is that of constructing a differential diagnosis. Although the clinical context and ancillary findings often suggest the cause of the pleural effusion, thoracentesis and appropriate examination of the pleural fluid are indicated in virtually every instance. Thoracentesis, in appropriate hands, is a safe procedure with limited morbidity. Precautions should be used in patients with a bleeding diathesis, very small effusions, or an obliterated pleural space as well as in those using anticoagulant drugs, in patients who are uncooperative, or if conditions are present that make even a small pneumothorax extremely hazardous. In these circumstances, the risk-to-benefit ratio of any procedure must be weighed carefully; in these instances, experienced personnel should perform the procedure, probably using ultrasound guidance. Although it is traditionally suggested that more than 1000 ml of fluid should not be removed at any one *sitting* to avoid reexpansion pulmonary edema, this is usually not the case. Procedures should probably be halted, however, if the patient begins to cough, has chest pain, or other possible signs of increasingly negative pleural pressure. Regardless, fluid should be removed slowly.

Numerous studies can be done on pleural fluid, and those required are dictated in large measure by the clinical context. If foul-smelling pus is obtained, for example, extensive biochemical analysis is not required; only Gram's stain and culture are needed. In most situations, however, fluid analysis is needed to distinguish transudates from exudates, because such distinction helps narrow the differential diagnosis. The key measures are lactate dehydrogenase (LDH), total protein, white blood count and differential, glucose, and pleural pH. An exudate is defined by any ONE of the following: ratio of pleural fluid to serum protein greater than 0.5; LDH ratio greater than 0.6; or LDH greater than two thirds of the normal serum value.

Exudates are characteristic of malignancy, parapneumonic effusions, and a variety of infectious and noninfectious inflammatory states. Acidosis (pH < 7.30) and reduced glucose (< 60 μg/dl) are characteristic of empyema and rheumatoid pleurisy, but can occur in other conditions such as pleural carcinomatosis and evolving parapneumonic effusions. Occasionally, elevated pleural fluid amylase suggests conditions such as esophageal rupture, pancreatitis, pancreatic pseudocyst, and, rarely, certain malignancies. The use of pleural cholesterol levels is still investigative, and no set of measures have yet replaced *Light's* criteria (LDH, protein) to differentiate exudates from transudates. If chylothorax is suspected, triglycerides and chylomicron analysis (by lipoprotein electrophoresis) should be requested; fluid is not always turbid or milky in these instances. Pleural fluid cytologic examination is indicated whenever neoplasm is suspected.

One point of particular interest has been the differentiation between a *benign* parapneumonic effusion and one requiring chest tube drainage (increasingly referred to as *a complicated parapneumonic effusion*). The need for drainage, in addition to antibiotic therapy, is indicated by a positive Gram's stain, culture, or the presence of pus in the pleural space (empyema). Drainage should also be considered if pleural fluid pH is below 7.10 or if pleural glucose is low and LDH is greater than 1000 g/L after excluding other diagnoses for these abnormalities (e.g., tuberculosis, rheumatoid arthritis, and pleural carcinomatosis).

The procedures described will provide a diagnosis for most pleural effusions. Collateral data and the ultimate result of cultures (e.g., for fungi, tuberculosis) will resolve an additional number. In some instances, however, additional procedures are warranted. A closed-needle biopsy of the pleura should be performed as part of the initial thoracentesis in cases in which granulomatous diseases or a neoplasm is suspected. Fiberoptic bronchoscopy can be considered, but is of no demonstrated value unless the chest x-ray study demonstrates some parenchymal or nodal abnormality, or is suggestive of bronchial obstruction.

In patients with an undiagnosed effusion, especially if exudative or if malignancy is suspected, thoracoscopy is a remarkably safe and commonly used diagnostic procedure. Thoracoscopy can be performed through a single access site, often under local anesthesia and using spontaneous ventilation and intravenous sedation, although the operating room setting, general anesthesia, and tracheal intubation are desirable in some cases where adhesions, loculations, or infection are suspected. Thoracoscopy permits direct visualization of the pleura and external surface of the lung, as well as biopsy of pleura and lung, pleural fluid removal, and pleurodesis. In cases of loculated effusions,

the adhesions can be lysed. Thoracoscopy is associated with less morbidity than open procedures. Operator experience is, as always, a key consideration.

Beyond thoracoscopy, open pleural biopsy under general anesthesia is required for those patients in whom other procedures have failed to provide a diagnosis or in those in whom contemplated lung biopsy poses special risk (e.g., pulmonary hypertension) and open exposure is required to assure hemostasis. Despite proceeding to thoracoscopy or open biopsy, a small number of effusions remain undiagnosed and either resolve or, subsequently, express themselves as neoplasm.

Treatment of pleural effusions is usually that of the underlying disease. Therapeutic thoracenteses, however, are often necessary in cases of a large effusion or when the patient has significant underlying parenchymal lung disease. Always note whether symptoms such as dyspnea, chest pain, or cough resolve after evacuation of the effusion. Patients with recurrent symptoms that coincide with recurrent fluid accumulation should be considered for pleurodesis. Only patients with a very limited survival (< 2–3 months) should continue to be treated by multiple large-volume thoracentesis. Special therapeutic approaches may be necessary in patients with malignant effusions, malignant mesothelioma, empyema, tuberculosis, hemothorax, or trapped lung.

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13. PNEUMOTHORAX

Henri G. Colt

The pleural space is located between the visceral pleura surrounding the lung and the parietal pleura lining the inside of the rib cage; it is occupied by a small amount of lubricating pleural fluid. Pleural pressure is negative compared with atmospheric pressure, which helps maintain lung inflation. If the parietal or visceral pleura is breached and the pleural space is exposed to atmospheric (positive) pressure, air enters the pleural

space (i.e., pneumothorax occurs), and the lung collapses inward toward the mediastinum. Any condition that impairs the structural integrity of either pleural membrane can produce a pneumothorax. The prognosis and management depend on the underlying cause. Pneumothorax is often categorized as (a) idiopathic or spontaneous, (b) iatrogenic, or (c) traumatic. Within each category, pneumothoraces can be either uncomplicated (usually unaccompanied by symptoms or prolonged air leak) or complicated (accompanied by symptoms, radiographic evidence of mediastinal shift, bleeding, or prolonged air leak).

Spontaneous (idiopathic) pneumothorax (SP) occurs in patients without a history of any event known to cause pneumothorax (e.g., trauma or intervention). It generally presents unexpectedly in an apparently healthy individual. Patients usually have no evidence of bullous lung disease on radiographic, thoracoscopic, or open surgical examination. Spontaneous pneumothoraces are categorized as secondary, when abnormal lung parenchyma is noted, either from underlying lung disease or by identifying bulla or blebs during radiographic or direct examination.

At least two different mechanisms can lead to spontaneous pneumothorax. One is a visceral pleural *tear* (i.e., a bronchopleural fistula) caused by rupture of a subpleural bleb or bulla or by a parenchymal process that erodes through the visceral pleura (e.g., necrotizing pneumonia). The second mechanism is partial bronchial obstruction that acts as a *check-valve*. Subsequent progressive hyperinflation of distal air spaces occurs until air eventually dissects along bronchovascular spaces into the hilus and mediastinum, leading to a pneumomediastinum. From there, air can also dissect through fascial planes in the neck, resulting in subcutaneous emphysema, or through visceral pleura into one (usually the right) or both pleural cavities, resulting in pneumothorax.

In a young, otherwise healthy individual without radiographic evidence of lung disease, SP usually results from the rupture of subpleural apical blebs or bullae. The peak incidence is between the ages of 20 and 30 years with a 4 : 1 male predominance and a predilection for tall, thin individuals. The incidence of SP has been reported to be increased in cigarette smokers, but this is a controversial issue.

In most cases, symptoms develop at rest; however, onset can be associated with strenuous activity in up to 20% of cases and with a forceful cough or sneeze in at least 5%. Spontaneous pneumothorax should always convey a high index of suspicion for the presence of intrinsic lung disease, particularly if pneumomediastinum is also present. Among the lung conditions often associated with pneumothorax are emphysema (particularly bullous emphysema), diffuse interstitial processes (e.g., eosinophilic granuloma, sarcoidosis, usual interstitial pneumonia, desquamative interstitial pneumonia, and the pneumoconiosis), necrotizing pneumonias (including tuberculosis), endometriosis (catamenial pneumothorax in women during menses), and the acquired immune deficiency syndrome (related to malnutrition or *Pneumocystis carinii* pneumonia and associated with prolonged air leaks and decreased survival).

Iatrogenic pneumothorax most commonly occurs after invasive thoracic procedures such as thoracentesis, transbronchial lung biopsy, and subclavian vein catheterization; however, it also can complicate virtually any invasive procedure involving the neck or abdomen (e.g., liver biopsy, transtracheal aspiration, intercostal nerve block, and even acupuncture). Iatrogenic pneumothorax can complicate positive pressure ventilation and, in this setting, can be life-threatening. The mechanism is usually a combination of partial bronchial obstruction caused by edema, secretions, and check-valve air entry leading to progressive alveolar expansion and rupture.

Traumatic pneumothorax can occur in the setting of penetrating or nonpenetrating chest trauma. The former generally presents no diagnostic problem; however, the latter should prompt a careful search for rib fracture, bronchial rupture, and esophageal injury. Rib fractures are associated with tears of the visceral pleura and pneumothorax; bronchial rupture is associated with deceleration injury; and esophageal rupture is often associated with mediastinal air entry. Pneumothorax can also result from abdominal trauma (e.g., abdominal stab, bullet wounds) and diaphragmatic tears.

The clinical manifestations of pneumothorax depend on its size, the clinical context in which it occurs, and the mechanism(s) involved. In tall, thin individuals with spontaneous rupture of apical pleural blebs, chest pain and dyspnea are common presenting

symptoms. The pain is usually of sudden onset and initially pleuritic in character. After a few hours, it often changes to a dull ache; spontaneous resolution of the pain can occur within 2 to 3 days. Approximately 10% of patients do not experience pain. Dyspnea occurs in 80%, often with spontaneous resolution within 24 hours despite persistence of the pneumothorax. Prominent coughing occurs in 10%; occasionally, it is the major or only symptom. Less than 5% of patients are asymptomatic. It is noteworthy that symptoms can be transient and do not correlate well with the radiographic size of the pneumothorax.

The most common physical findings are tachypnea, splinting, and decreased inspiratory expansion of the involved hemithorax, a tympanitic percussion note, decreased fremitus, and decreased breath sounds on the involved side. In patients with a check-valve mechanism, the initial complaint of substernal pressure or discomfort is often interpreted as cardiac in origin. Subsequently, the patient can experience chest pain, dyspnea, and relief of the substernal symptoms if pneumothorax or decompression into cervical subcutaneous tissues occurs. Mediastinal emphysema can be detected on auscultation by the presence of a mediastinal *crunch* (Hamman's sign) coincident with cardiac systole and diastole. Dyspnea can be exaggerated and persistent when underlying lung disease is present. In severely traumatized or mechanically ventilated patients, symptoms and signs can be obscured or difficult to interpret. This is also the case in patients with emphysema who have severe hyperinflation and diminished breath sounds. An electrocardiogram may show nonspecific ST-T wave changes and axis shifts, suggesting myocardial or thromboembolic disease.

The diagnosis of pneumothorax is usually made on clinical history and review of chest radiographs. In some cases, it may be necessary to obtain end-expiratory chest films to visualize the pleural reflection of the collapsed lung. Although the diagnosis is usually made easily by careful inspection of chest radiographs and comparisons with previous films, in some cases detection may be difficult. Settings where radiographic diagnosis can be problematic include patients with small loculated pneumothoraces, on mechanical ventilation, and with known bullous lung disease. In some cases, computed tomographic (CT) scanning may be necessary for diagnosis. CT scans can be used to document or identify unilateral or bilateral bullous abnormalities during or after episodes of pneumothorax. CT scans can also be helpful to guide chest tube drainage in patients with complex, uniloculated or multiloculated penumothoraces, and to help differentiate pleural air collections from bullous air collections. This is important to avoid inadvertently inserting chest tubes into lung bullae.

Complications of pneumothorax are classified as *acute* and *long-term* and can occur in all types. Acute complications include tension pneumothorax, acute respiratory failure, bilateral pneumothorax, hemothorax, and pyothorax. Long-term complications include failure to reexpand (i.e., persistent pneumothorax) and recurrence.

Tension pneumothorax, which can appear rapidly and, if untreated, result in death, is caused by continued air entry into the pleural space. The persistent accumulation of *positive* pressure within the pleural cavity results in substantial lung collapse, mediastinal shift toward the contralateral side, and even compression of the uninvolved lung. This situation can occur following rupture of an apical bleb if the visceral pleural tear forms a *flap* (i.e., opening with inspiration and closing with expiration). Tension pneumothorax also can occur following rupture of the mediastinal pleura caused by intrapulmonary *check-valving* if air continues to be pumped into the mediastinum. This situation is made worse if the patient is receiving mechanical ventilation and in some cases of cardiopulmonary resuscitation. It can also occur after penetrating chest wounds when air may continue to enter the chest with each inspiration, especially if check-valving at the site of chest wall injury prevents expulsion of air during expiration. Patients with indwelling chest tubes for pneumothorax with acute deterioration may also have suspected tension. In these cases, the chest tube may not be communicating adequately with the area of air leakage (because of adhesions, plugging of the chest tube itself, or chest tube malfunction).

A diagnosis of tension pneumothorax should be considered in the setting of (a) progressive dyspnea and tachycardia, (b) shift of the trachea and mediastinal structures away from the involved side, and (c) increasing tympany of the involved side. Roent-

genograms can confirm those events, but, if suspected, immediate decompression by transthoracic insertion of a needle attached to a syringe may be indicated. If a patient has a chest tube in place already and the development of a tension pneumothorax is suspected, all bandages should be removed and the tube carefully inspected. Waiting for radiographic confirmation may be fatal.

Bilateral pneumothorax is a rare event that usually is not detected without a chest roentgenogram. Reinflating one lung with a chest tube usually maintains patient stability until this complication is recognized.

Pneumothorax can be accompanied by hemothorax and pyothorax. In these cases, patients are said to have a *hydropneumothorax*. Evacuation of the pneumothorax and evaluation of the pleural effusion are mandatory. Hemothorax, often caused by adhesion rupture, lung parenchyma, or vascular structures is potentially lethal because the pleural space easily accommodates a large amount of blood and because tamponade of the bleeding site may not occur. In the presumably healthy individual who develops an SP, discovery of pleural effusion is an indication for diagnostic thoracentesis to exclude bleeding. Effusions occur in about 20% of patients and are nonbloody; however, radiographic obscuring (i.e., *blunting*) of the costophrenic angle requires the presence of at least 100 ml of fluid. In the otherwise healthy individual, such bleeding is more common with recurrent pneumothorax and is caused by rupture of vascular adhesions between visceral and parietal pleura. If tamponade does not occur, a patient can exsanguinate rapidly from such a *benign* source. Bleeding sites in other forms of pneumothorax are much more variable, but the same rule applies—thoracentesis should be performed on all effusions to exclude hemothorax. Pyothorax, on the other hand, usually results from the entry of organisms along with air. Rare in SP not associated with preexisting lung disease, it is much more common with lung rupture caused by necrotizing pneumonia or penetrating trauma. The symptoms and findings are the same as those of an empyema.

The management of pneumothorax depends on the setting in which it occurs. Patients with uncomplicated SP and no underlying lung disease have four reasonable treatment options: (a) observation (inpatient or outpatient); (b) aspiration by needle or by a small-lumen catheter; (c) insertion of a small chest tube or catheter attached to a one-way flutter valve; or (d) insertion of a chest tube attached to water seal (*closed*) or suction drainage. Of these, aspiration is the least effective and may lacerate the lung and introduce infection. The traditional practice in the United States is either to hospitalize for observation of complications or to insert a chest tube for 1 to 3 days, or both. Both large- and small-bore chest tubes are readily attached to one-way flutter devices (Heimlich valves) that allow ambulation and discharge. Patients with hydropneumothorax, however, should probably not be treated with one-way valves because of the risk of obstruction from viscous fluid or blood. Careful exclusion of patients at risk for developing significant complications (e.g., the presence of underlying lung disease, heart disease, advanced age) is essential for the safety of such outpatient approaches.

Insertion of a small catheter followed by aspiration may be all that is needed for therapy of a pneumothorax attributed to introduction of air during a procedure involving the chest wall (e.g., thoracentesis, central venous pressure insertion). In most other categories of pneumothorax, institute prompt chest tube insertion and closed drainage of the abnormal air collection. The more severe the underlying lung disease and clinical dysfunction, the more urgent the indication for tube drainage. It is noteworthy that none of the usual treatments for primary spontaneous pneumothorax attempts to erradicate the cause of the pneumothorax or help determine its cause.

Patients with unexplained recurrent spontaneous pneumothoraces, persistent bleeding into the pleural space, or in whom tube drainage has not resulted in reexpansion of the lung, warrant thoracoscopic examination of the pleura and lung. This procedure allows complete inspection of underlying lung parenchyma, identification of air leaks, and closure using endoscopic stapling devices, loop ligation, or electrocauterization of blebs and bullae. Pleurodesis can also be performed using talc insufflation, chemicals, or pleural abrasion.

Thoracotomy may be necessary for some patients with pneumothorax. In these cases, a muscle-sparing axillary thoracotomy is usually possible. Hemothorax also may

require exploration or repair of the bleeding site. Failure to reexpand the collapsed lung with tube drainage is another indication for thoracoscopy or thoracotomy. The length of time necessary for a visceral pleural tear to heal and for lung reexpansion to occur during tube drainage depends on the particular patient and the severity of underlying disease. For example, patients with the human immunodeficiency virus, active *Pneumocystis carinii* pneumonia, and those on corticosteroids may be at increased risk for prolonged air leak with its associated increased risk for morbidity and mortality. In general, leaks persisting for more than 7 to 10 days rarely seal without surgical intervention.

Recurrence rates in otherwise healthy patients range from 10% to 50%. Approximately 60% of patients with a second recurrence will develop a third episode; after three episodes, recurrence exceeds 85%. Therefore, thoracoscopy or thoracotomy is usually recommended after the first recurrence and, increasingly, in patients with air leaks persisting for more than 3 to 5 days.

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14. HEMOPTYSIS

Henri G. Colt and Jack L. Clausen

Hemoptysis (i.e., coughing up blood), which is a frightening event for both healthcare providers and patients, occurs in a variety of clinical conditions. The amount and quality of this sign can range from blood-streaked sputum to several cupfuls of blood to even massive exsanguination. Death is rare and usually results from asphyxiation and respiratory arrest associated with flooding of the tracheobronchial tree. Indeed, massive hemoptysis is a life-threatening medical emergency that often cannot be controlled simply by endotracheal intubation and mechanical ventilation.

The incidence of hemoptysis reflects the incidence of the underlying disease and the patient population type (e.g., surgical, medical). In the United States, the most common causes are chronic bronchitis, bronchiectasis, and bronchogenic carcinoma, followed by tuberculosis, fungal infections, bacterial pneumonia and abscess, and pulmonary infarction. Less common conditions that cause hemoptysis are mitral stenosis, Goodpasture's syndrome, endobronchial foreign bodies, bronchial adenoma, pulmonary arteriovenous (AV) fistulas, Wegener's granulomatosis, cystic fibrosis, lymphangioleiomyomatosis, and, rarely, coagulopathies. Recent data suggest an increased risk for hemoptysis in patients with indwelling airway stents who can develop airway inflammation, granulation tissue overgrowth, and erosion of tracheobronchial mucosa.

The approach to diagnosis and initial management of patients has not changed; the clinician is generally faced with the same questions:

1. Where is the bleeding coming from (the lungs, the airways, nasopharynx, or the digestive tract)?
2. Can the bleeding be stopped?
3. Will the bleeding recur at some time in the future?
4. Does the patient have a systemic disease that predisposes to bleeding?
5. Is emergency intervention needed and what kind of surveillance should be instituted?

The anatomic source of bleeding depends on the specific pathologic process. Data from bronchial artery embolization studies indicate that bronchial arteries and collaterals from axillary, intercostal, diaphragmatic, and other systemic arteries of the thorax are the source of bleeding in most cases. Inflammation associated with infection and carcinoma can cause reactive hypervascularity of bronchial arteries and stimulation of collaterals. Localized inflammation also can result in erosion of these hypervascular networks of vessels and bleeding. Pulmonary arteries, capillaries, and veins are the source of hemoptysis in fewer than 10% of cases.

The hemoptysis found in chronic bronchitis arises from superficial vessels in the bronchial mucosa. Hemoptysis associated with chronic fibrocavitary disorders arises from rupture or erosion of enlarged bronchial arteries and bronchopulmonary anastomoses. Development of pulmonary artery aneurysms and rupture from vessel wall invasion can occur in tuberculosis. In mitral stenosis, the primary sites of bleeding are bronchial veins with blood supplied from both bronchial arteries and reversed blood flow from pulmonary veins.

All instances of hemoptysis require careful evaluation to determine the cause and site of bleeding. The history often is invaluable and establishes the duration and extent of bleeding, prior episodes, and the presence of known cardiopulmonary or other diseases. It is extremely important to differentiate hemoptysis from hematemesis and nasopharyngeal bleeding. The physical examination provides specific clues to the diagnosis (e.g., an oronasopharyngeal bleeding site, microtelangiectasia, pulmonary or cardiac findings). The chest radiograph may suggest the cause and location of the hemoptysis. The characteristic finding of blood in the air spaces is a confluent or patchy alveolar filling pattern that becomes reticular over days and clears in 3 to 10 days. However, an infiltrate may represent blood aspirated from another bleeding site elsewhere in the lungs, making precise localization of a bleeding site problematic. A negative chest radiograph is common, and computed tomography (CT) scans generally are not helpful.

Other relevant laboratory studies include a complete blood count; smear, culture, and cytologic examination of the sputum; and, when appropriate, arterial blood gas analysis, as well as perfusion (Q) and ventilation (V) lung scans if pulmonary emboli are suspected. Perfusion scans are not useful in localizing a bleeding site. A number of studies have found an elevated single-breath diffusion capacity (DLCO) in a high proportion of patients with intrapulmonary bleeding, although it does not appear that DLCO plays a useful role in the diagnosis or care of most patients (except, possibly, in patients with suspected Goodpasture's syndrome).

Fiberoptic bronchoscopy (FOB), the most valuable diagnostic technique, should be used for all patients with hemoptysis of uncertain cause. Bronchogenic carcinoma has been detected in 2% to 13% of patients with hemoptysis and a normal chest radiograph. Foreign bodies, bronchial adenoma, and other causes of bleeding can be identified readily, and the site of the bleeding usually can be determined.

Although the need for FOB in evaluating hemoptysis is clear, the timing of the procedure in the face of active bleeding is controversial. Although early bronchoscopy is desirable because it minimizes the likelihood that the site will go undiscovered when bleeding has stopped, no evidence indicates that delaying FOB for 24 or 48 hours will adversely affect the ultimate outcome (e.g., detection of operable carcinoma). FOB should be performed carefully, however, and operators should be ready to handle massive bleeding by having large-channel bronchoscopes available for suctioning; equipment for emergency intubation, sedation, and ventilation; and, preferably, capacity and ability to perform rigid bronchoscopy. Operators should also be familiar with the use of tamponade balloons. Operators should recognize that cough induced by the procedure can promote more bleeding and that blood can spread through the tracheobronchial tree during the procedure, thereby obscuring the bleeding site.

Arteriography and embolization of bronchial and related collateral vasculature (e.g., intercostal, axillary, and subclavian arteries) are playing an increasingly useful role in the treatment of hemoptysis that is not responsive to conservative measures. Initially, this technique was only a temporizing measure until patients could undergo lung resection; now many experienced clinicians believe it plays a primary role for long-term control of recurrent or persistent hemoptysis (e.g., recurrent episodes of more than 200 ml/d) even in patients who might be candidates for resectional surgery. Patients who are particularly suitable are those with diffuse lung disease in whom bleeding can arise from more than one site, and those who are not candidates for surgery. Actual visualization of a *bleeding blush* during arteriography is rare. Localization is inferential from the visualization of the abnormal vascularity of reactive bronchial arterial networks; hence, previous specific localization by FOB is important. Inadvertent embolization of spinal arteries is a significant complication, but uncommon if care is exercised in identifying possible spinal arteries branching from vessels considered for embolization. A number of series have reported initial control in 80% to 90% of cases with long-term recurrences in 10% to 25%. Recanalization or growth of new bronchial vessels can limit the permanence of this therapeutic procedure in some patients. Although infusion of sclerosing liquids or small embolic particles is appealing because of the theoretic advantages of occlusion of flow distal to collateral feeder vessels, the incidence of bronchial wall necrosis, spinal artery occlusion, and intense acute chest pain precludes the use of these agents currently.

Therapy for hemoptysis varies with bleeding severity, the specific cause of bleeding, and the overall condition of the patient. The three goals of therapy are to prevent asphyxiation, stop the bleeding, and treat the primary cause. If the volume of hemoptysis is large (>200 ml/d) or if the patient has minimal respiratory reserve, an emergency situation exists. The first goal of therapy is to identify the bleeding site, stop the bleeding, and prevent aspiration of blood into other major airways. In experienced hands, FOB will identify the bleeding site. In some cases of massive bleeding, rigid bronchoscopy is warranted. If necessary, tamponade balloons can be inserted and left in place for hours or days while the patient is stabilized and readied for resectional therapy, although coughing can dislodge the balloon. If therapeutic embolization of bronchial arteries is contemplated (see below), placing a Fogarty balloon may allow time for the prerequisite angiographic studies.

Another approach to protecting functional airways involves placing a special endotracheal tube with an inflatable distal cuff into the nonbleeding right or left main stem

bronchus. The use of a double-lumen tube permits adequate suctioning of blood. However, placement of the tube requires experienced personnel. When available, bronchial arteriography with embolization is increasingly being used for patients with massive hemoptysis who do not respond to more conservative measures. Recent improvements in angiographic techniques have minimized the potential complications of spinal artery occlusions. The efficacy of temporizing measures such as iced saline lavage and Fogarty balloon placement is dependent on local expertise; the role of intravascular infusions or topical applications of vasoconstrictor agents (e.g., vasopressin) has not been established. Reports of successful treatment of bleeding pulmonary aspergilloma by percutaneous intracavitary infusion of amphotericin are anecdotal.

Surgical resection of any bleeding site requires its identification and a patient able to tolerate thoracotomy. Occasionally, patients require emergency surgery before a diagnosis has been established, particularly in some patients with massive hemoptysis. In an often-quoted older study, Crocco et al. found that the mortality of patients with massive hemoptysis (i.e., 600 ml of blood/16-hour period) treated medically was 75%. Among similar patients treated by surgical resection, the mortality was 23%. An especially high mortality rate in patients treated medically was also observed in the setting of massive hemoptysis associated with lung abscesses. The high mortality rate associated with conservative medical therapy may reflect the bias of a nonrandomized study and a patient population with advanced tuberculosis and multiple disease processes; other studies have found comparable mortality rates between conservative medical management and surgical resection. Nevertheless, experience supports the role for surgical resection if all efforts to control bleeding medically (e.g., strict bed rest, no chest percussion or spirometric testing, aggressive cough suppression) are unsuccessful and embolization of bronchial artery and related vessels is either not available or unsuccessful in controlling bleeding.

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15. ASPIRATION

Richard A. Bordow

Inhalation of foreign material from the nasopharynx or stomach can result in a variety of closely related, yet distinct, clinicopathologic syndromes known as *aspiration pneumonia*. Several conditions predispose individuals to these syndromes including (a) states of impaired consciousness;, (b) circumstances or drugs impairing swallowing or coughing; (c) use of nasogastric or endotracheal tubes; (d) tracheostomy; and (e) anatomic abnormalities such as tracheoesophageal fistula and gastric outlet obstruction. Aspiration of gastric contents is relatively common and can occur without demonstrable consequence in healthy persons and during general anesthesia (7% to 16%) and endoscopy of the upper gastrointestinal tract (25%). All forms of aspiration pneumonia are more common in the dependent portions of the lung, as might be predicted. The most common manifestations of pulmonary aspiration are chemical pneumonitis, pleuropulmonary infections, and acute airway obstruction.

The classic form of chemical aspiration is acid aspiration pneumonia (Mendelson's syndrome), first described in pregnant women. In this group, the major risk for morbidity and mortality is obstetric surgery and general anesthesia. The degree of pulmonary injury varies according to the volume, distribution, and pH of the aspirate. Large, widely distributed aspirates with a pH less than 2.5 are associated with higher injury and mortality rates. Pathologic examination within the first few hours reveals hemorrhagic pulmonary edema and patchy microatelectasis free of bacterial contamination. The diagnosis may be difficult to prove unless either the aspiration is witnessed or gastric contents are visualized directly in the airway or suctioned from an endotracheal tube. The most important clinical features are severe dyspnea (usually within 2 hours), wheezing, rales, rhonchi, cyanosis, tachycardia, and hypotension. A low-grade temperature may be present (33%). Severe hypoxemia is common, occurring in association with a normal or low arterial $Paco_2$, a wide alveolar-arterial oxygen difference, and a marked reduction in compliance. Chest roentgenograms reveal diffuse multilobar infiltrates that can be alveolar or interstitial. Occasionally, the roentgenographic pattern of pulmonary edema is seen; however, the absence of cardiac enlargement and

pulmonary venous hypertension should suggest a noncardiogenic cause. Pleural effusion is rare.

Management of patients with acid aspiration is similar to that of those with adult respiratory distress syndrome. Patients require immediate supplemental oxygen and hemodynamic stabilization. Tracheal intubation and mechanical ventilation generally are necessary and, in conjunction with the use of positive end-expiratory pressure, may moderate lung injury. Fiberoptic bronchoscopy should be performed if particulate aspiration is visualized or suspected. Bronchial lavage is of no benefit, because the effect of acid is immediate and its absorption occurs within minutes. Prophylactic antibiotics are not recommended; however, if evidence of infection supervenes (e.g., persistent fever, purulent sputum, progressive abnormality on chest roentgenogram), appropriate antibiotics should be administered. The value of corticosteroid administration remains controversial. The prevalent attitude, however, is that steroids are of no benefit and should not be used because they may predispose to more serious infection or other complications. In earlier series, the mortality rate was high, ranging from 30% to 60%; however, today the prognosis is probably improved as a result of improved methods of critical care. Pulmonary aspiration during labor is largely preventable by simple measures: (a) at risk parturients should limit oral intake; (b) anesthesia should be administered with the assumption of a full stomach; (c) conduction anesthesia is preferred over general anesthesia; and (d) administration of prophylactic agents (e.g., antacids, histamine$_2$ receptor antagonists, dopamine antagonists) should be considered to raise the pH and decrease the volume of gastric contents.

Aspiration of bacteria from infected nasopharyngeal contents, the most common form of aspiration pneumonia, can lead to necrotizing pneumonia, empyema, and lung abscess. Aspiration pneumonia is the most common cause of death in the elderly. The most frequent bacterial pathogens isolated in nonhospitalized patients are anaerobic organisms resembling *mouth flora* (e.g., *Fusobacterium nucleatum, Peptostreptococcus* spp., and *Prevotella melaninogenicus*); in hospitalized patients, mixed facultative anaerobes and aerobic organisms, particularly *Klebsiella* spp., *Staphylococcus aureus, Streptococcus* spp., and *Haemophilus influenzae* are common. Aspiration of mouth anaerobes does not typically cause pneumonia because these organisms are generally less virulent. Aspiration can lead to pneumonia if either (a) large amounts of oropharyngeal secretions are aspirated or (b) chronic infections in the gingivodental crevice increase the concentration of anaerobic bacteria in the mouth. Patients with acid aspiration can develop secondary bacterial infections caused by aerobic gram-positive and gram-negative organisms, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Aspiration may be caused by liquids (e.g., fresh or salt water, hydrocarbons, or mineral or vegetable oils) or particulates. Individuals who survive the immediate threat of drowning in salt or fresh water can develop respiratory failure; however, the severity of this syndrome generally is less than that caused by acid aspiration (see Chapter 86).

Aspiration of hydrocarbons most commonly occurs in children who have accidentally ingested kerosene, furniture polish, or gasoline. Lung complications can follow direct aspiration (e.g., during vomiting) or gastrointestinal absorption (and subsequent toxicity as the bloodborne hydrocarbon traverses the lung). Pulmonary symptoms are usually mild, and the prognosis is excellent with supportive management. Gastric lavage should be avoided, because it can increase the potential to aspirate. Some evidence suggests that steroids may be useful in the acute stage of this syndrome, but this remains unproved.

Aspiration of mineral and vegetable oils leads to a chronic form of lipoid pneumonia. Patients are frequently elderly individuals who use oil-containing agents; they may complain of mild dyspnea, cough, and sputum production. Pediatric patients with constipation who have been treated with mineral oil can also develop similar problems. These agents may not elicit a normal protective cough reflex and can impair mucociliary transport. These effects can increase the likelihood of aspiration and impair clearance from the respiratory tract. A thorough history with specific questions regarding the use of nosedrops and laxatives may suggest the diagnosis. The chest roentgenogram reveals interstitial infiltrates or, on occasion, one or more mass lesions that may suggest tumor. Pathologic examination of lung tissue may demonstrate oil-laden or fat-laden macrophages, but these findings are not specific for this syndrome.

Bronchoalveolar lavage (BAL) and gas chromatography, mass spectrometry, or both can demonstrate the exogenous origin of the lipid. Appropriate therapy includes withdrawal of the offending agent and treatment of any secondary infection.

Aspiration of particulate material can obstruct airways and lead to a necrotizing pneumonia, depending on the particle size. Large particles can obstruct the trachea or main stem bronchi and cause rapid suffocation and death. This condition is often referred to as the *cafe coronary syndrome* because of its propensity to occur in restaurants in association with choking on large pieces of meat. The Heimlich maneuver has been widely publicized as an effective method to dislodge the foreign material. Smaller particles such as teeth or peanuts can occlude smaller bronchi and result in an acute pneumonia or a chronic inflammatory process simulating a lung tumor, distal to the obstruction. Early bronchoscopy by either flexible or rigid instrumentation is indicated for removal of the foreign body; after a few days, inflammatory reaction and fibrotic organization make these procedures less successful.

Aspiration of small (nonobstructing) food particles can lead to a hemorrhagic pneumonia. The degree of injury (and mortality) is greater with larger volumes, as in acid aspiration. In contrast to acid aspiration, the symptoms and pulmonary changes occur later and intense bronchial transudation is not seen. In addition, the $Paco_2$ is usually higher than in acid aspiration, with the degree of hypoxemia about the same. The frequency and natural history of this form of aspiration pneumonia are poorly characterized because few studies have considered food particle aspiration as a separate entity.

The treatment of aspiration pneumonias is largely supportive; therefore, prevention is of paramount importance. Patients with a depressed state of consciousness are at greatest risk and should receive special attention. They should not be placed in the head-down position, and drugs that induce vomiting should not be given. Nasogastric tubes should not be placed unless without good airway control. Patients with gastric atony (e.g., diabetic ketoacidosis) or intestinal ileus should be continuously drained via nasogastric tubes. Antibiotic treatment should be guided by appropriate bacteriologic studies; however, the most common antibiotic regimens are penicillin, clindamycin, and the combination of metronidazole plus penicillin. Finally, it should be recalled that narcotic antagonists, frequently used in the approach to drug overdose, can induce vomiting; consequently, airway control should be secured before their administration in comatose patients.

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16. MIDDLE LOBE SYNDROME

Beat Walder and James H. Harrell II

Middle lobe syndrome is defined as recurrent or chronic atelectasis of the right middle lobe (RML). A variety of benign and malignant conditions have been reported as causative factors. All age groups are affected. The peculiar propensity for the RML to collapse is partially explained by several anatomic features: (a) the RML bronchus usually originates as a narrow and often slitlike lumen; (b) the RML bronchus is surrounded by lymph nodes draining both middle and lower lobes, and inflammatory conditions or tumors can enlarge these nodes and compress the bronchus; and (c) the RML is usually separated by fissures and by a pleural envelope from the upper and lower lobes, which may impair collateral ventilation to the RML.

In RML syndrome not related to malignancy, lung pathology at resection most commonly demonstrates bronchiectasis and bronchiolitis. Atelectasis, granulomatous inflammation, or abscesses can be found in the distal airspaces. The postulated sequence of events starts with a bronchitis or pneumonitis. Secretions generated by inflammation may not be cleared effectively because of poor collateral ventilation. Airway occlusion occurs and atelectasis develops. Inflammatory enlargement of lymph nodes surrounding the bronchus can lead to bronchial compression, further promoting lobar collapse. In some patients, the RML atelectasis persists; in others, the RML reexpands as inflammation resolves, either spontaneously or with treatment, and the lymph nodes decrease in size. However, minor endobronchial abnormalities can persist, leading to recurrent episodes of inflammation and atelectasis.

Patients with RML syndrome frequently present with a history of recurrent pneumonitis. Symptoms include chronic cough, low-grade fever, hemoptysis, chest pain, wheezing, and dyspnea. When total RML collapse is present, physical findings are scant. Before collapse, scattered rales and evidence of consolidation may be present in the anterior chest over the RML. Chest radiographic findings depend on stage of the recurrent atelectasis cycle. Initially, a RML infiltrate may be present. When total collapse occurs, the minor fissure may no longer be visualized on the posteroanterior view because the RML collapses medially against the cardiac shadow. Absence of a previously visible fissure and obliteration of the adjacent heart border may be the only diagnostic clues on the posteroanterior view. On the lateral view, however, the collapsed RML appears as a linear density that must be distinguished from an intrafissural effusion. Once the lobe re-inflates, the chest radiograph may be normal, and the minor fissure reappears.

Computed tomography scanning (CT) of the chest may reveal more detailed information than standard chest radiography about the distribution and presence of intrathoracic lymphadenopathy, the central airways, and other concomitant lesions. CT can be especially useful in evaluating patients at risk for malignant RML syndrome or documented malignant RML syndrome.

Recognition of the RML syndrome requires an understanding of the different stages of the disease process. In some cases, the diagnosis can be delayed in the presence of an underlying disease (e.g., asthma) that produces similar symptoms. Once the diagnosis of middle lobe syndrome is considered, clinical and laboratory evaluation is indi-

cated to identify any underlying condition or concurrent infection. Bronchoscopy should be performed to evaluate RML airway patency and obtain specimens for pathologic and microbiological studies. In addition, therapeutic lavage can be beneficial to remove inspissated secretions, mucoid plugs, and debris. Bronchoscopic examination reveals benign stenosis or tumor in approximately 40% of patients and will be normal or nonspecific in the rest.

Benign RML syndrome is most commonly associated with lung infection and asthma. Influenza caused by *Haemophilus* organisms and streptococcus pneumonia are the most common isolates; rarely, typical and atypical mycobacterial or fungal infections are identified. Microbiologic cultures are commonly sterile, possibly because of antecedent antimicrobial therapy. Asthma is reported as a frequent underlying disease of RML syndrome in children. The reported incidence of documented bacterial infections in asthmatic children with RML syndrome varies widely (from almost none to 43%).

Bronchoscopic examination will be normal or show mild mucosal abnormalities in most patients with benign RML syndrome. In a minority, bronchoscopic examination may reveal bronchial obstruction from a number of causes (e.g., foreign body aspiration, endobronchial sarcoidosis, bronchial stenosis, or broncholithiasis). Both the underlying condition predisposing to RML syndrome and intercurrent or superimposed infections should be treated. This approach will minimize further injury to the RML. Conservative therapy is successful in most patients with benign RML syndrome. Surgical therapy is considered only when conservative measures fail; recurrent hemoptysis is a frequent indication for resection.

Malignant RML syndrome, which has been reported in up to 43% of patients with RML syndrome, may be caused by primary and metastatic tumors. Squamous cell carcinoma is the most common histologic type. Malignant RML syndrome commonly presents with bronchial obstruction from either endobronchial or submucosal disease or extrinsic compression. However, bronchoscopic examination can be negative or nondiagnostic in malignant RML syndrome in up to 22% of patients; further evaluation, including invasive testing (e.g., percutaneous lung biopsy, mediastinoscopy; occasionally thoracotomy), may be needed to establish the diagnosis.

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17. COMPLICATIONS FOLLOWING PULMONARY RESECTION

David P. Kapelanski

Thorough preoperative evaluation and preparation for lung resection is the most effective way to minimize postoperative complications. Specific objectives include (a) assessment of the extent and consequences of parenchymal resection required for disease management; (b) determination of concurrent cardiac and pulmonary status; (c) recognition and amelioration of disorders that might compromise postoperative ventilatory mechanics such as malnutrition and reactive airway disease; and (d) reduction in tracheobronchitis by smoking cessation. Postoperative pain can reduce spontaneous ventilatory volume and interfere with effective coughing, thereby promoting retention of secretions. Consequently, prudent preoperative planning should include selecting an operative approach that minimizes disruption of chest wall mechanics whenever possible. Furthermore, because respiratory depression can limit postoperative narcotic administration, regional analgesic techniques should be considered. Recent experience with lung volume reduction surgery suggests that safe anatomic or wedge resection is often possible, even in higher risk patients with scrupulous preoperative preparation, with meticulous intraoperative technique, careful anesthetic management, and exacting postoperative care. *It should be emphasized that all physicians who care for patients following lung resection surgery should be aware of the common and unusual complications that can arise in this setting.*

Bleeding can occur during and after lung resection. During an operation, knowledge of variation in segmental pulmonary anatomy and avoidance of intemperate dissection in inflamed tissue provide the best prophylaxis against catastrophic hemorrhage that may not be manageable without sacrificing lung parenchyma. The risk of perioperative hemorrhage can be reduced further by circumspect introduction of pleural drains and pericostal sutures. Finally, meticulous inspection of the hemithorax before wound closure facilitates opportune management of previously unappreciated mediastinal or pleural bleeding points.

Postoperative pleural effusion is relatively common. Following resection, the volume drained by pleural catheters is highly variable but is rarely more than 300 ml in the initial 24 hours unless significant pulmonary inflammation is present at operation. Whenever pleural drainage exceeds a rate of 200 ml/h for 2 or more hours or 100 ml/h for 4 or more hours, reexploration should be considered. Clinical factors that should encourage a more aggressive approach to reoperation include the development of hemo-

dynamic instability, radiographic evidence of retained intrapleural blood, or difficulty obtaining blood components that may be required either to sustain oxygen delivery or correct coagulation system defects.

Atelectasis is a common complication following thoracotomy. The frequency of postresectional atelectasis can be reduced by preoperative management of purulent tracheobronchitis and bronchospasm; several studies suggest that even short periods of tobacco abstinence can be beneficial. Following operation, adequate analgesia is essential to facilitate maintenance of normal ventilatory volumes and effective secretion clearance. Properly coached incentive spirometry, intermittent positive pressure breathing, and encouragement of early ambulation are useful. If airway secretions are copious or cough ineffectual, mucolytics, chest physiotherapy, and careful nasotracheal aspiration can be instituted. Although lobar or segmental collapse may be evident after careful clinical examination of a patient with fever, tachypnea, or desaturation, radiographic diagnosis is important. When clinically significant, atelectasis is best treated by bronchoscopy, which permits rapid evacuation of secretions and early reexpansion. If a prolonged problem is anticipated, minitracheostomy may be useful.

Bronchial stump integrity following resection *should be* routinely tested under saline during sustained inflation to an airway pressure of 25 to 30 cm H_2O. Continuous air leaks should be repaired immediately. Following partial lung resection, low-volume air leaks from residual parenchyma are common but can be minimized if caution is exercised during the development of intersegmental and interlobar planes. Reinforcement of parenchymal staple lines with glutaraldehyde fixed bovine pericardial strips or bovine collagen should be considered whenever undertaking resection in an abnormal lung. Major parenchymal air leaks identified at operation should be carefully repaired with absorbable suture; pedicled or free pleural flaps or bovine pericardium and collagen can be used to buttress the repair when the pulmonary parenchyma is diseased. Massive air leak occurring within the initial 24 hours of operation suggests a failure of surgical technique because of unrecognized injury to pulmonary parenchyma or airway dehiscence. *Bronchoscopy and reoperation should be strongly considered to prevent the development of empyema or the need for prolonged pleural drainage.* Most postoperative air leaks resolve within 96 hours of operation without adjunctive maneuvers, provided the residual lung fills the hemithorax. If a low-volume air leak persists beyond this time, the integrity of the drainage system should be confirmed. In the absence of a postresection space, increasing the magnitude of pleural suction has limited value and can perpetuate the leak. Partially withdrawing the pleural catheters may displace drainage apertures from raw parenchymal sites and allow fusion of these sites with adjacent tissue. Chemical sclerosis and autologous blood patches are both used with variable success in the management of low-volume leaks. If these relatively simple interventions fail and hospitalization is prolonged beyond 1 week for the sole purpose of managing an air leak, a Heimlich valve can be substituted for the water seal system, with further management on an outpatient basis.

The management of postresectional spaces depends on the extent of resection. A postresectional space following pneumonectomy is unavoidable; following lesser resections, the remaining parenchyma *may only partially fill* the hemithorax. In ordinary circumstances, the residual space will be obliterated or minimized with some combination of compensatory mediastinal shift, hemidiaphragmatic elevation, and narrowing of the intercostal spaces. These mechanisms can fail in the presence of pulmonary or visceral pleural restriction or if mediastinal mobility has been reduced by prior inflammatory disease or preoperative radiation therapy. Improperly positioned or managed pleural drains, postoperative atelectasis, and prolonged air leaks are all factors that further contribute to incomplete expansion of the residual parenchyma. Although most postresectional spaces are clinically innocuous, it is hazardous to assume that all will resolve in benign fashion. If a significant space is recognized as inevitable at the conclusion of a limited resection, myoplasty or osteoplastic or tailoring thoracoplasty each merit consideration, particularly when operation is undertaken in the management of infectious disease. Pleural tents are more readily created, but their utility largely resides in their capacity to help seal parenchymal air leaks.

Following operation, maneuvers to prevent or manage atelectasis are paramount. It is relatively simple to increase the magnitude of suction on pleural drains, although

the response is unpredictable. Therapeutic pneumoperitoneum, which is used less frequently, can be useful, particularly in the presence of a persistent air leak. If the pleural drains are patent and an uninfected space remains after cessation of any postoperative air leak, suction should be discontinued. If the residual space is stable and the air leak does not recur after 24 hours on water seal drainage, the pleural tubes should be withdrawn. If the space enlarges or the air leak recurs, a brief additional trial of suction is generally warranted, if still within the initial 2 weeks of operation. Failure at that juncture warrants management by conversion to an open drainage system and secondary consideration of space reduction by myoplasty or thoracoplasty, especially if the volume of the residual space is large and the duration of open drainage likely to be unduly prolonged.

A bronchopleural fistula complicating pulmonary resection generally develops in the second week following operation and is usually heralded by fever, hemoptysis, and increased cough. Preoperative treatment of malnutrition and tracheobronchitis and careful intraoperative management of the bronchus during dissection and closure are essential to minimize the risk of fistula. A recurrence or delayed increase in the magnitude of postresectional air leak, the late development of subcutaneous emphysema, or the recurrence, enlargement, or new development of a postresectional space should each be assessed with this potential development in mind. The most pressing management goals are protecting the residual parenchyma from soilage and preserving adequate minute ventilation.

The first goal is met by promptly reestablishing closed pleural drainage; following pneumonectomy, the patient should be positioned with the operated side dependent until the pneumonectomy space has been drained. A balanced drainage system prevents excessive mediastinal shift and, thus, confers some advantage in the initial management of early postpneumonectomy bronchopleural fistula; if such is not readily available, a standard water seal system will ordinarily suffice. Suction should not be done in an unbalanced system if mediastinal stability is questionable. The resumption of pleural drainage can secondarily unmask a high-volume air leak, particularly in the setting of positive pressure ventilation; the consequent ventilation maldistribution can precipitate respiratory compromise. Under these circumstances, the most expediently available method to reestablish effective tidal ventilation should be employed. Following pneumonectomy, this generally dictates selective intubation of the remaining main stem bronchus; following lesser resections, insertion of a dual-lumen tube is preferable. Bronchoscopy is indicated whenever a bronchopleural fistula is suspected. Careful examination of the bronchial stump will generally confirm the diagnosis, although a smaller fistula can elude detection. If early reoperation to close the fistula is a consideration, the viability of the bronchial mucosa at potential sites of stump revision or more proximal resection should be verified. A fibrin glue patch, applied at the time of bronchoscopy, may seal small-caliber fistulas. Myoplastic closure is increasingly preferred for definitive management of a bronchopleural fistula.

The capacity of the patient to withstand additional parenchymal resection following lobectomy, segmental resection, or bronchoplasty must be determined, because debridement of the initial repair and reclosure may not always be possible. If the patient's medical condition is tenuous or the success of early repair is questionable, it is prudent to deliberately temporize and maintain closed drainage. A small proportion of fistulas will seal without further intervention. If, after stabilization, myoplastic repair is not considered to be an option, an Eloesser flap should be created.

Infection of the pleural space following pulmonary resection can be minimized by careful adherence to the principles of operative preparation, operative technique, and postoperative care described above. Although postpneumonectomy empyema can occur several months or years following operation, most are diagnosed during the second postoperative week. Diagnostic features include enlargement or development of new air-fluid levels in the postresectional space, accompanied by constitutional symptoms and signs of infection. Aspiration of the pleural fluid under ultrasound or radiographic guidance may be necessary if pleural drains are no longer present.

Reestablishing effective pleural drainage is the first therapeutic goal once the diagnosis of empyema has been verified. Closed irrigation of the empyema space with antibiotic solutions, coupled with systemic antibiotics, may sterilize the space and allow sub

sequent removal of the pleural catheters without further intervention. If this technique fails and the patient is judged a suitable candidate to withstand a major operative procedure, myoplastic obliteration of the space should be considered. An Eloesser flap is generally used in those instances in which medical circumstances preclude a more aggressive approach.

Lobar torsion can occur whenever a lung lobe is peripherally untethered. Operative division of the pulmonary ligament and completion of the anatomic fissures may permit unconstrained rotation of a retained lobe about the bronchovascular pedicle, with infarction the ultimate consequence. Careful examination of lobar orientation during tidal ventilation is required before chest closure. Unusual mobility of a remaining lobe should be restricted, either by fixation to adjoining mediastinal tissue or by peripheral attachment to an adjacent lobe. Following operation, clinical and radiographic signs may not permit discrimination between torsion, atelectasis, or parenchymal hematoma. The diagnosis is readily confirmed by bronchoscopy. Immediate reoperation may allow salvage of the involved lobe; if recognition or operation is delayed, lobectomy is required.

Inadvertent obstruction of pulmonary venous return or interruption of both pulmonary and bronchial arterial circulation can cause lobar or segmental gangrene in the absence of torsion. Arterial insufficiency, although less common, is generally not recognized until infarction or gangrene has developed, whereas venous compromise may be recognized at operation. Immediate resection of the involved segments is imperative whenever the diagnosis of gangrene is established.

Cardiac herniation is a rare problem that can develop if the pericardium is breached during pneumonectomy. Herniation, which generally occurs shortly after the operation is concluded, is characterized by the precipitous development of systemic venous obstruction and cardiovascular collapse. Immediate reoperation is mandatory to reintroduce the heart into the pericardial sac and restore effective circulation. A generous pericardiectomy prevents cardiac entrapment following left but not right pneumonectomy; thus, right-sided defects are best managed by closure using autologous tissue or prosthetic material. If available tissue is inadequate and prosthetic material undesirable, the pericardial edges can be carefully sutured to the adjacent atrial and ventricular epicardium.

The postpneumonectomy syndrome is an infrequent problem caused by extreme mediastinal shift following right pneumonectomy or, in the presence of a right aortic arch, following left pneumonectomy. Malacia of the trachea or main stem bronchus as a result of compression between the aorta and pulmonary artery can cause dyspnea and recurring pulmonary infections. Interventions to eliminate the compression have been successful when malacic changes are not severe.

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    Comprehensive and timely discussions of each of the topics discussed in this brief chapter. Essential resources for anyone managing patients with thoracic disease.

18. KEY PULMONARY SYMPTOMS: COUGH AND DYSPNEA

Michael S. Stulbarg

Cough and dyspnea are the key symptoms of pulmonary disease. Virtually all conditions involving the respiratory system can present with dyspnea, whereas cough occurs in a more limited spectrum. Understanding these symptoms is important for appropriate evaluation and management. In general, the diagnosis of dyspnea is easier than the diagnosis of cough.

Cough usually results from reflex stimulation by mucus, foreign material, stretch, or inflammation of irritant neuroreceptors located in the vocal cords, trachea, and airways. Similar receptors are present in the ear canal, nose, sinuses, pericardium, diaphragm, esophagus, and stomach, but their role is less clear. Afferent impulses travel to the brain via the trigeminal, glossopharyngeal, superior laryngeal, and vagus nerves; efferent signals are then transmitted to the glottis, intercostals, and abdominal muscles, culminating in (a) inspiration, (b) glottic closure, (c) diaphragmatic relaxation, and (d) active contraction of the expiratory muscles (intrapleural pressure usually rises to 100–200 mmHg). When the glottis suddenly opens, the large transpulmonary pressure gradient between the pleura and the airway results in the explosive release of intrathoracic air (i.e., a cough). Expiratory volume is no greater than during a forced exhalation, but narrowing of the airway caused by the pressure gradient leads to a high linear velocity (close to the speed of sound) which is generally effective in dislodging mucus and foreign materials. Patients with airway obstruction produce normal intrathoracic pressures but generate lower linear velocities and a less effective cough because of airway narrowing.

Occasional cough caused by minor irritations (e.g., aspiration of oral secretions) is normal. Cough accompanying upper or lower viral respiratory tract infections may continue for 6 to 8 weeks; beyond that time, further evaluation may be warranted. Chronic cough is a nonspecific symptom of a heterogeneous group of diseases that can (a) alter mucus quantity or quality (e.g., chronic bronchitis, parenchymal infection, some tumors); (b) increase sensitivity of cough receptors (e.g., asthma, cigarette smoking); (c) inadequately protect against acid stimulation of the esophageal mucosa (i.e., esophageal reflux) or cause actual aspiration of food or oral secretions (e.g., gastric reflux, neurologic dysfunction); (d) stimulate cough receptors directly (e.g., foreign body, tumor, thyroiditis, or thyromegaly) or indirectly (e.g., interstitial lung disease, pulmonary edema); or (e) affect psychological health. Cough can cause severe complications, including sleep disruption, rib fractures, emesis, stress incontinence, syncope, and social isolation.

Dyspnea is the clinical term for the discomfort associated with effort in breathing (e.g., bronchospasm) or the urge to breathe (e.g., hypoxemia, hypercapnia.) It is a visceral sensation somewhat analogous to hunger or nausea and results from neural activity within the part of the cerebral cortex responsible for sensory perception. Dyspnea arises from stimuli that have different neurophysiologic pathways (e.g., exercise, breath-holding, hypoxemia), but all have in common stimulation of the respiratory center. The greater the respiratory center stimulation (e.g., with hypoxia plus acidosis, pulmonary hypertension, pulmonary infiltrates), the greater the dyspnea. At the same time, anything that weakens respiratory muscles (e.g., thyrotoxicosis, myopathy) or puts them at mechanical disadvantage (e.g., hyperinflation, pleural effusion) will increase dyspnea. Other factors can affect the perception of dyspnea (e.g., belief about its significance, emotional state, airway inflammation, distraction). Dyspnea can be considered part of the warning system for humans to know when they are at risk of receiving inadequate ventilation. Dyspnea may be normal (e.g., with exercise), but patients with a variety of diseases experience it at lower than normal levels of physical activity.

The cause of cough or dyspnea is often apparent following a careful history, physical examination, and chest x-ray study. Some historical data are key (e.g., smoking history or occupational exposures), but historical data (e.g., timing, frequency, aggravating factors, and presence of sputum) have been shown not to be as helpful as previously thought. However, information about prior or current responses to empiric treatment (e.g., antibiotics, corticosteroids) can be especially helpful. Cough following an upper respiratory illness may be considered *normal* for up to 2 months and is probably caused by transient bronchial hyperreactivity or injury to airway receptors. Hyperreactivity persisting beyond 2 months may indicate asthma. Symptoms caused by occult asthma can be triggered by nonspecific irritants such as cold air, fumes, or smoke as well as by specific allergens. Nocturnal cough or dyspnea is frequently caused by asthma, esophageal reflux, or congestive heart failure. A personal or family history of allergies increases the probability that unexplained symptoms may be caused by asthma. Although chronic cough occurs in up to 75% of cigarette smokers, a changing pattern of cough or sputum production in this population should prompt evaluation for occult malignancy. Some patients cannot

distinguish a true *chest cough* from *throat clearing*. Frequent throat clearing, rhinorrhea, *sinus congestion*, or a feeling of *drainage* in the back of the throat suggests a diagnosis of postnasal drip or sinusitis. Cough caused by chronic bronchitis may be indistinguishable from that of bronchiectasis, although classically the latter is associated with more sputum production. Bronchiectasis can be quiescent for years until reactivated by a viral infection. Bronchiectasis may become evident in midlife because of chronic infection by *Mycobacterium avium* complex, particularly in women. Cough associated with blood-streaked sputum requires consideration of endobronchial malignancy, although it is usually caused by airway infection. Dyspnea from chronic lung or heart disease usually increases with exertion and improves with rest. Obesity increases ventilatory demands and, thereby, dyspnea for any activity. Cachexia of any cause can weaken respiratory muscles and increase dyspnea. Dyspnea or cough independent of activity or exposure should raise the possibility of psychogenic causation.

A thorough physical examination can provide clues to the cause of cough or dyspnea. The patient's appearance may suggest a diagnosis (e.g., obesity, cachexia, central cyanosis, and use of accessory muscles). A nasal quality to the voice may suggest sinus disease. Hoarseness or inspiratory stridor suggests laryngotracheal disease. The sound of the cough can be helpful: (a) a *musical* cough suggests asthma; (b) a *wet* cough suggests airway infection; and (c) a *brassy* cough suggests tracheal narrowing. Upper airway examination should include a search for (a) hairs or impacted cerumen impinging on the tympanic membrane; (b) nasal secretions, bogginess, or polyps (rhinitis); (c) oropharyngeal cobblestoning or mucopurulent secretions (postnasal drip); and (d) tenderness over the maxillary sinuses (sinusitis). Examination of the neck may reveal unexpected masses or an enlarged thyroid pressing on the trachea. Auscultation may reveal wheezing, rhonchi, or rales, which are suggestive of chronic obstructive pulmonary disease, interstitial lung disease, or heart failure. Unilateral wheezing on forced inspiration or expiration may be caused by a partially obstructing endobronchial lesion (e.g., tumor, foreign body, mucus plug). A negative finding on chest examination does not exclude primary lung disease. Keys to occult cardiac disease include jugular venous distention as well as gallops and murmurs.

Diagnosis of either cough or dyspnea often requires supplemental laboratory and radiologic tests. The persistence and severity of the symptom will determine the extent of testing needed. Simple laboratory screening may uncover anemia, renal failure, or eosinophilia, each of which will lead to a different diagnostic pathway. Elevation of the sedimentation rate is nonspecific but may lead to diagnosis of collagen vascular disease (e.g., giant cell arteritis), malignancy, or chronic infection (e.g., sinusitis).

The pulmonary function laboratory testing can be very useful in making a diagnosis. Spirometry can reveal airflow limitation or a decrease in vital capacity. More complete pulmonary function testing with measurement of lung volumes and diffusing capacity may suggest restrictive or pulmonary vascular diseases. Bronchoprovocation testing with histamine or methacholine may uncover occult asthma, but such testing should not be performed within 2 months of a viral syndrome because hyperreactivity is considered a *normal* consequence of viral infection during that period. Cardiopulmonary exercise testing with measurements of arterial blood and expired gases may uncover exercise-induced hypoxemia, cardiac ischemia or arrhythmias, and ventilatory limitations to exercise.

Imaging studies beyond the chest x-ray may also be important. Sinus computed tomography (CT) scans are far more sensitive than sinus x-ray studies for the diagnosis of sinusitis, which can be found even in the absence of signs or symptoms. CT scanning of the chest is useful for the diagnosis of occult tumors, infiltrates, or adenopathy. High resolution chest CT scanning is increasingly helpful in identifying occult emphysema, bronchiectasis, interstitial lung disease (including infection), and even pulmonary emboli. High resolution CT has largely replaced gallium scanning in the search for occult parenchymal lung disease (e.g., pneumocystosis). The diagnosis of esophageal reflux can be elusive and requires esophagoscopy with biopsy or overnight pH monitoring. Occult heart failure can present with dyspnea, cough, or both; diagnosis may require evaluation of ventricular function with echocardiography or even cardiac catheterization. Ultimately, bronchoscopy should be performed to exclude an endobronchial process

(e.g., tumor, foreign body, broncholith, stenosis) in any patient with a persistent cough. Bronchoscopy or ear, nose, and throat evaluation may reveal paradoxical vocal cord motion, which usually is not recognized unless it is included in the differential diagnosis. The diagnosis of psychogenic cough or dyspnea is one of exclusion and should only be considered when a clear impact on emotional status of the symptom is seen or after all other diagnoses have been excluded. A small group of patients with chronic cough or dyspnea cannot be diagnosed. In such patients, reassurance and surveillance for development of disease are important.

The treatment of cough or dyspnea is most effective when directed to a specific condition, but clinicians often give empiric therapy rather than subject a patient to an expensive and complex diagnostic algorithm. The severity and persistence of the symptom will determine when to abandon empiric trials and pursue a more aggressive workup. A trial of antihistamine-decongestants, bronchodilators, inhaled corticosteroids, antireflux therapy, or other medications may be appropriate for both diagnosis and treatment; specific algorithms have been proposed. Antihistamines and decongestants can be helpful, especially in the patient with chronic rhinorrhea or nasal stuffiness, but vasoconstrictor solutions should be avoided as they can lead to rebound rhinitis. Topical nasal steroids are sometimes effective in the treatment of postnasal drip (i.e., chronic rhinitis or sinusitis), even in the absence of a history of allergy or of laboratory evidence of eosinophilia. Oral leukotriene antagonists and nasal or inhaled cromolyn or nedocromil may be helpful, particularly if allergy is playing a role. Oral antibiotics are indicated if cough is associated with purulent sputum; prolonged or cyclic treatment may be necessary for sinusitis or bronchiectasis. Empiric trials of oral corticosteroids are often given because of the severity of the symptom. When a clear-cut clinical response occurs, it is not unreasonable to continue therapy, but the dosage should be reduced as much as possible. Partial response should lead to the search for multiple causes, which may need to be treated in a stepwise manner to achieve an adequate clinical response.

Nonspecific recommendations for cough treatment can include hydration, steam inhalation, expectorants (e.g., guaifenesin), lozenges, and mucolytic drugs, but their benefits have not been scientifically established. Attempts at cough suppression with dextromethorphan or opiates (e.g., codeine) have not been shown to be dangerous as long as side effects (e.g., sedation, constipation) are considered and a search for the underlying cause continues. In an occasional patient with persistent cough, oral benzonatate perles or nebulized lidocaine (e.g., 5 ml. of 4% solution) sometimes provides substantial relief. As diagnosis of dyspnea is generally easier than diagnosis of persistent cough, nonspecific recommendations are required less frequently. Strategies for dyspnea control can include supplemental oxygen, education (e.g., optimal use of medications, avoidance of triggers), distraction, social support, breathing control techniques (e.g., pursed lips breathing), or an exercise program. Education and an exercise program are generally best given in a pulmonary rehabilitation program, if available.

As intractable cough or dyspnea can be debilitating, narcotics should be used compassionately, as for severe pain, with appropriate attention to tachyphylaxis, dependence, and side effects.

Cough

1. Buist AS, et al. The effect of smoking cessation and modification on lung function. *Am Rev Respir Dis* 1976;114:115.

   Evidence that even after many years of smoking, cessation of smoking will dramatically reduce cough and sputum production.

2. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;300:633.

   Classic description of the cough variant of asthma, established by demonstration of bronchial hyperreactivity and response to bronchodilators in the absence of the usual stigmata of asthma (e.g., wheezing, airflow limitation).

3. Pylypchuk GB. ACE inhibitor—versus angiotensin II blocker—induced cough and angioedema. *Ann Pharmacother* 1998;32:1060.

   Meta-analysis of 10 studies showing that the new angiotensin receptor blockers do not cause cough as do the angiotension-converting enzyme (ACE) inhibitors.

4. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;141:640.

Enthusiastic presentation of the anatomic diagnostic protocol made famous by the lead author. A specific cause of cough was determined in 101 of 102 patients: one cause in 73%, two in 23%, and three in 3%. Postnasal drip syndrome was a cause 41% of the time, asthma 24%, gastroesophageal reflux 21%, chronic bronchitis 5%, and bronchiectasis 4%. Cough was often the sole presenting manifestation of asthma (28%) and reflux (43%). Of note, methacholine challenge was falsely positive 22% of the time, although my experience has not been as encouraging.

5. Sen RP, Walsh TE. Fiberoptic bronchoscopy for refractory cough. *Chest* 1991;99:33.

Bronchoscopy provided a diagnosis in 7 of 25 patients with chronic unexplained cough.

6. Sevelius H, Colmore JP. Objective assessment of antitussive agents in patients with chronic cough. *Journal of New Drugs* 1966;6:216.

The measurement of cough frequency obtained from a questionnaire given to patients correlated poorly with cough counts obtained from a tape recording.

7. Weiss W, Seidman H, Boucot KR. The Philadelphia Pulmonary Neoplasm Research Project. Symptoms in occult lung cancer. *Chest* 1978;73:57.

Symptoms are seldom useful in the detection of lung cancer, but the appearance of changing expectoration and chronic cough in older male smokers should raise a suspicion of the disease.

8. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;160:406.

Eosinophilic bronchitis is an important newly recognized cause of cough. It presents with chronic cough and sputum eosinophilia (>3%) without abnormal spirometry or bronchial hyperreactivity and responds to inhaled corticosteroids. In this study, eosinophilic bronchitis was the final diagnosis in 12 of 91 patients referred for unexplained cough. After treatment with inhaled budesonide (400 μg twice daily) cough improved and sputum eosinophilia fell from 16.8% to 1.6%.

9. Luque CA, Vazquez Ortiz M. Treatment of ACE inhibitor-induced cough. *Pharmacotherapy* 1999;19:804.

ACE inhibitors continue to be important drugs for cardiovascular disease. This article reviews options when the drugs cannot safely be discontinued.

10. Palombini BC, et al. A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest* 1999;116:279.

Yet another group finds that some combination of asthma, gastroesophageal reflux, and postnasal drip explains most (i.e., here 93.6%) chronic coughs and suggests that this be known as the pathogenic triad for chronic cough.

11. Tam TW, Bentsi-Enchill A. The return of the 100-day cough: resurgence of pertussis in the 1990s. *Canadian Medical Association Journal* 1998;159:695.

Several recent articles, including this one, have emphasized that approximately 20% to 25% of patients with persistent cough have culture or serologic evidence of Bordetella pertussin *infection. These infections usually respond to macrolide therapy.*

12. Lawler WR. An office approach to the diagnosis of chronic cough. *Am Fam Physician* 1998;58:2015.

Up-to-date review article with a well-described algorithmic approach to diagnosis of cough.

13. Irwin RS, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998; 114:133S-181S.

Consensus panel report on the diagnosis and treatment of cough. Highly recommended.

14. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax* 1998;53:963.

This is one of numerous articles emphasizing the high correlation between esophageal reflux and cough. This study emphasizes that fundoplication can be dramatically helpful in people who have failed proton pump therapy. Unfortunately, no

single standard exists for making this diagnosis, although 24-hour pH monitoring appears to be the best test.

15. Pratter MR, et al. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;119:977.

An excellent article outlining an algorithmic approach to cough, initially using antihistamine-decongestant combination therapy, which was beneficial in 39 of 45 patients and the only treatment needed in 16. Methacholine challenge had a negative predictive value of 100% and a positive predictive value of 74% for cough caused by asthma. Recurrence of cough at 3 months was common (18%).

16. Trochtenberg S. Nebulized lidocaine in the treatment of refractory cough [see comments]. *Chest* 1994;105:1592.

Convincing case report of prolonged treatment of refractory cough with nebulized lidocaine. Mild dysphonia was the only side effect.

Dyspnea

17. Zeppetella G. The palliation of dyspnea in terminal disease. *American Journal of Hospice and Palliative Care* 1998;15:322.

An overview of the management of dyspnea in the terminally ill.

18. Demertzis S, et al. Lung volume reduction surgery for severe emphysema. *J Cardiovasc Surg (Torino)* 1998;39:843.

One of several reports that lung volume reduction surgery is a promising treatment for selected patients with end-stage emphysema. A large multicenter study funded by Medicare and the National Institutes of Health is currently underway.

19. Mahler D. Dyspnea. In: Lenfant C, ed. *Lung Biology in Health and Disease*. Vol. 111. New York: Marcel Dekker; 1998.

A recent monograph on dyspnea. Well worthwhile for those seriously interested in the symptom.

20. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1877.

Disappointing results from a trial of oral morphine for dyspnea in patients with severe dyspnea. Doses were high enough to cause side effects, thus, inadequate dosing was not the cause of lack of benefit. This does not exclude the appropriateness of morphine for treatment of dyspnea in the terminally ill.

21. Cross JJ, et al. A randomized trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. *Clin Radiol* 1998;53:177.

A randomized trial of patients with suspected pulmonary embolism that concludes that $\dot{V}/\dot{Q}$ scanning should be replaced by spiral CT scanning. Results are provocative but $\dot{V}/\dot{Q}$ scanning is not obsolete yet.

22. Ferrari K, et al. Chronic exertional dyspnea and respiratory muscle function in patients with chronic obstructive pulmonary disease. *Lung* 1997;175:311.

Demonstrates that the level of chronic exertional dyspnea in chronic obstructive pulmonary disease increases as the ventilatory muscle derangement increases. Unfortunately, therapeutic interventions to improve ventilatory muscle function are limited.

23. O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med* 1997;155:530.

Evidence is provided that oxygen relieves dyspnea in chronic obstructive pulmonary disease, by reducing both ventilatory demand and blood lactate.

24. Lacasse Y, et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease [see comments]. *Lancet* 1996;348:1115.

Meta-analysis of 10 studies showing that the new angiotensin receptor blockers do not cause cough as the ACE inhibitors do.

25. Mahler DA, Franco MJ. Clinical applications of cardiopulmonary exercise testing. *J Cardiopulm Rehabil* 1996;16:357.

Nice review of the utility of cardiopulmonary exercise testing in the workup of dyspnea.

26. Carrieri-Kohlman V, et al. Exercise training decreases dyspnea and the distress and anxiety associated with it. Monitoring alone may be as effective as coaching. *Chest* 1996;110:1526.
Evidence that exercise training alone is a powerful treatment for dyspnea.
27. Dyspnea. Mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med* 1999;159:321.
The best review article available on the subject of dyspnea per se. *This consensus statement presents a physiologic approach to understanding the mechanisms of the symptom and a physiologic approach to its treatment.*

19. THE LUNG IN PREGNANCY

Ann M. Romaker

Pregnancy is characterized by a series of dynamic physiologic changes that can have an impact on multiple organ system functions. It is associated with a variety of changes in pulmonary anatomy and physiology and, by itself, predisposes to several pulmonary disorders.

The anatomic alterations of pregnancy include increases in (a) the level of the diaphragm (3–4 cm); (b) the transverse diameter of the chest (2 cm); and (c) the subcostal angle (68–103 degrees). These changes take place earlier than can be accounted for by the enlarging uterus. Additionally, capillary engorgement throughout the respiratory tract results in mucosal edema and hyperemia. Multiple biochemical alterations occur concomitantly; progesterone, estrogen, prostaglandin, corticosteroid, and cyclic nucleotide levels rise during the course of pregnancy. The multiple functional consequences of these alterations are not clear, but the increased progesterone is thought to be responsible for the hyperventilation observed during pregnancy. The absolute rise in free cortisol (two to three times baseline levels) can modify the course of some steroid-responsive respiratory diseases.

Pulmonary function tests reveal multiple deviations from the nonpregnant state. Lung volumes are altered: functional residual capacity (FRC) diminishes by 10% to 25% because of diaphragmatic elevation, which in turn is associated with an 8% to 40% fall in expiratory reserve volume and a 7% to 22% fall in residual volume. Vital capacity and total lung capacity are preserved, although at term a slight drop occurs in total lung capacity. Because the motion of the diaphragm and the inspiratory muscles is preserved, inspiratory capacity actually increases about 10% and tidal volume increases about 28%. Changes in flow rates have not been observed, although airways resistance appears to fall. In general, closing volume remains unchanged (individual variations are reported). A normal closing volume coupled with a low FRC may result in airway closure near or above FRC.

During pregnancy, minute ventilation rises markedly; this rise is mainly accomplished by an increase in tidal volume. Consequently, the resting $Paco_2$ drops to 27 to 32 mmHg. The pH is usually maintained by an increased renal excretion of bicarbonate, with a fall in serum bicarbonate to 18 to 21 mEq/L. The decline in $Paco_2$ leads to a rise in Pao_2. The alveolar to arterial oxygen gradient also rises, possibly related to airway closure at or near FRC.

Pregnancy also results in an increased value of the respiratory quotient, possibly related to an increased utilization of carbohydrate, and an increased resting oxygen consumption paralleling an increase in body weight. No differences have been noted in the response to mild to moderate exercise in the pregnant versus the nonpregnant state. During sleep, no significant difference in arterial oxygen saturation is seen in pregnancy. Apneas and hypopneas, however, may appear or worsen in obese women during their pregnancies.

Approximately 60% to 70% of women complain of dyspnea during the course of pregnancy, generally in the first or second trimester. Dyspnea usually improves near term, suggesting that mechanical factors are not responsible. Dyspnea appears to be related to the increased minute ventilation.

Pregnant women suffer from respiratory diseases more than their age-matched, nonpregnant counterparts. An increased mortality is associated with influenza and varicella infections and an increase in primary varicella pneumonias. Pregnant women do not have a higher risk for bacterial pneumonia than nonpregnant women. It should be stressed that pregnancy is not a contraindication to chest radiography if it is clinically indicated. Radiation exposure sustained during a standard chest film is 50 mrad to the chest and 0.0025 to 0.005 cGy to the gonads. The minimal dose related to adverse effects on the fetus is considered to be 0.01 to 0.05 Gy. Nevertheless, appropriate lead shielding should be provided.

Pregnancy exerts little effect on the natural history of tuberculosis. The indications for treatment and recommended primary drug regimens are unchanged. Although isoniazid and rifampin cross the placenta, extensive experience indicates that these agents are not teratogenic. In addition, adverse effects have not been demonstrated with ethambutol. Both streptomycin and ethionamide, however, have been associated with fetal abnormalities.

The course of asthma during pregnancy is unpredictable. If severe disease antedates pregnancy and the expected fall in immunoglobulin E concentrations during pregnancy do not occur, clinical deterioration can develop. In a review of 1059 pregnancies, Turner et al. found 49% experienced no change in their disease during pregnancy, 29% improved, and 22% worsened. In general, the care of the pregnant patient does not differ from that of nonpregnant asthmatics. Extensive experience with methylxanthines and beta-agonist bronchodilators, as well as corticosteroids, has not demonstrated adverse outcomes during pregnancy. Data suggest that untreated asthma has a more deleterious effect on the outcome of pregnancy than the judicious use of these drugs.

Several reports have documented an improved or unchanged pulmonary status during pregnancy among women with sarcoidosis. In general, the chest radiograph remains normal throughout pregnancy if the disease had cleared before conception; if it was resolving before pregnancy, improvement continues. Patients with inactive interstitial fibrotic disease remain stable during pregnancy. Those with active interstitial inflammatory disease often manifest partial or even complete clearing on their chest x-ray films. Unfortunately, most of these patients subsequently experience an exacerbation of their disease within 3 to 6 months postpartum.

Several other lung conditions are associated with pregnancy. Rib fractures can occur during the last trimester. These fractures are most often preceded by a chronic cough and are the result of mechanical factors related to an increasing abdominal volume. The lower ribs are pushed upward into a more horizontal position by the abdomen and pulled out by the intercostal and oblique muscles, thereby exerting a great force in the opposite direction. An asynchronous pull caused by an acute burst of coughing probably results in the so-called *cough fracture*. The differential diagnosis of thoracic pain should also include pulmonary embolism, pneumothorax, and acute intervertebral disk disease.

The risk of thromboembolic disease appears to be primarily associated with the postpartum period rather than with pregnancy. Several large studies have reported a pregnancy-related incidence of deep venous thrombosis of 1.2% and of pulmonary embolism of 0.2% to 0.4%. Despite its infrequency, pulmonary embolism is second only to abortion as a cause of maternal death. Doppler ultrasonography and impedance plethysmography are most helpful in the first and second trimesters. However, an accurate diagnosis is important, given the potentially disastrous consequences of a missed diagnosis and because of the difficulties associated with therapy.

The diagnosis of deep venous thrombosis is difficult to make in pregnant women; tests can pose significant risk to the fetus (venography, radiolabeled fibrinogen) or fail to detect thrombosis in pelvic veins. *D*-dimmer levels may be helpful diagnostic aids, although they can rise up to 50% during the last trimester. Warfarin (Coumadin)

crosses the placenta, producing both fetal hemorrhage and congenital abnormalities. Heparin can be safely used up to and immediately after labor, because it does not cross the placenta. However, the risk of excessive bleeding remains a consideration. Estimates of radiation exposure to the fetus for the various procedures available to diagnose deep venous thrombosis and pulmonary embolism are listed in Table 19.1.

Amniotic fluid embolism, which is peculiar to pregnancy, accounts for 4% to 10% of total maternal mortality. Because this condition carries a mortality risk of greater than 80%, it demands prompt recognition. Death is often immediate, or it can occur within several hours of labor and delivery. Clinical features include respiratory distress syndrome, cardiovascular collapse, and disseminated intravascular coagulation. Predisposing factors include a tumultuous labor, the use of intrauterine stimulants, the presence of meconium in the amniotic fluid, advanced maternal age, multiparity, and intrauterine fetal death. Treatment is supportive, as no specific therapy yet exists.

The effects of scuba diving on pregnancy are unclear. As this sport increases in popularity, more and more physicians are consulted regarding its suitability for the pregnant woman (e.g., How dangerous is decompression sickness? What are the effects of the decompression chamber to the fetus and mother?). In a study of pregnant ewes, bubbles in the placenta were demonstrated at depths greater than 60 feet. In a more relevant but retrospective study of 208 female divers, no increased risk of abortion or fetal abnormalities was noted. It is currently suggested that women of childbearing age limit their dive to 60 feet and to a duration of one half the limits of the US Navy decompression tables. Additionally, they should avoid strenuous dives, hypoventilation, and chilling.

Premature labor occurs in approximately 7% to 10% of deliveries. Systemic tocolysis of these patients has produced dramatic improvements in fetal survival but has also resulted in sometimes life-threatening maternal complications. Noncardiogenic pulmonary edema has been reported with most tocolytic agents, including magnesium sulfate, terbutaline, and ritodrine. The incidence is low, approximately 3%, and appears to be higher in the presence of coexisting maternal infection. Other risk factors include multiple gestations, hydramnios, hypertension, and the use of glucocorticoid steroids. Treatment involves cessation of tocolytic therapy, antibiotics, if clinically indicated, and aggressive support.

Table 19.1. Estimates of amount of radiation absorbed by the fetus for different procedures

Procedure	Estimated fetal radiation (cGy)
Bilateral venography without abdominal shield	0.628
Unilateral venography without abdominal shield	0.314
Limited venography, abdomen shielded	<0.050
Pulmonary angiography via femoral route	0.405
Pulmonary angiography via brachial route	<0.050
Perfusion lung scan using ^{99m}Tc MAA	
3 mCi	0.018
1–2 mCi	0.006–0.012
Ventilation lung scan	
Using ^{133}Xe	0.004–0.019
Using ^{99m}Tc DTPA	0.007–0.035
Using ^{99m}Tc SC	0.001–0.005
Radioisotope venography	0.205
Radioactive fibrinogen uptake scanning	2.000
Chest radiography	<0.001

From: Ginsberg JS, et. al. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. *Thromb Haemost* 1989; 61:189; with permission.

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2. Bernard J, et al. Pulmonary mechanics during pregnancy. *J Clin Invest* 1967; 46:945.
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5. Esplin MS, Clark SL. Outpatient management of asthma during pregnancy. *Clin Obstet Gynecol* 1998;3:5551998.
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6. Even-Tov I, et al. Stress fractures of ribs in late pregnancy. *Int Surg* 1979;64:86.
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8. Gaensler EA, et al. Pulmonary function in pregnancy: serial observations in patients with pulmonary insufficiency. *American Review of Tuberculosis* 1953; 67:779.
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A collection of articles reviewing common pulmonary problems in pregnancy.
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20. HYPERBARIC OXYGEN THERAPY

Paul Cianci

Hyperbaric oxygen (HBO) therapy is the intermittent administration of 100% oxygen at pressure greater than sea level. The technique can be implemented in a walk-in (multiplace) chamber, compressed to depth with air, in which the patient breathes 100% oxygen through a mask, head tent, or endotracheal tube. Alternatively, the patient can be treated in a monoplace (one-person) chamber pressurized with 100% oxygen. In either case, the arterial partial pressure of oxygen will approach 1500 mmHg at a pressure equivalent of 33 feet of seawater.

During the 1930s, oxygen at pressure was proposed as a treatment for decompression sickness (*the bends*). In the early 1960s, Dutch investigators showed the efficacy of HBO in the treatment of gas gangrene and anemic states. Later in that decade, it became the standard therapy for US Navy diving casualties. Subsequent studies have shown the importance of oxygen in the treatment of problem wounds, enhancement of white cell killing ability, preservation of compromised tissue, and angiogenesis. Some centers are using this modality in the treatment of acute thermal injury. The clinical indications for the use of HBO as an adjunct to traditional medical and surgical regimens continue to be expanded and redefined.

The indications for HBO include gas embolism, carbon monoxide poisoning, crush injury and acute traumatic ischemia, decompression sickness, gas gangrene, clostridial myonecrosis, necrotizing anaerobic infections, osteomyelitis (refractory), radiation necrosis, osteoradionecrosis, hard- and soft-tissue radiation injury, compromised skin grafts and flaps, enhancement of healing in selected problem wounds, exceptional blood loss anemia, intracranial abscesses, and thermal burns. The mechanism of action of HBO relates to its ability to deliver substantial increases of oxygen to hypoxic peripheral tissue. Oxygen inhaled at pressure dissolves in plasma. At 3 atm, an arterial Po_2 of nearly 2200 may be achieved. Up to 6.9 volumes percent of oxygen can be forced into solution, a quantity sufficient to maintain life in the absence of hemoglobin. Exposure to oxygen at pressure causes a 20% reduction in blood flow, resulting in less diapedesis and bleeding in areas of capillary damage and a reduction of edema. The tenfold increase in oxygen content of plasma more than compensates for decreased arterial flow.

Tissue oxygen levels play a major role in the physiology of wound healing, white cell function, and blood flow. Abnormally low tissue Po_2 is often present in nonhealing tissue (5–15 mmHg). This results in diminished white blood cell (WBC) killing and decreased collagen synthesis by fibroblasts. Raising tissue oxygen tensions to 30 to 40 mmHg provides the substrate necessary to lay down a collagen matrix for support of capillary ingress into avascular or damaged areas. HBO can increase tissue oxygen tensions to levels consistent with efficient WBC killing of bacteria, fibroblast production of collagen, and stimulation of angiogenesis. A necessary prerequisite is the ability to deliver plasma to the area through an intact circulation. Although treatments are usually 90 to 120 minutes once or twice daily, tissue O_2 levels remain above baseline values for some time. This is especially true in ischemic tissue, which can act as an oxygen capacitance system.

Hyperbaric oxygen therapy is the treatment of choice for decompression sickness and arterial gas embolism caused by diving accidents or iatrogenically induced gas embolism (e.g., lung biopsy or invasive vascular procedures). HBO compresses bubbles and results in counterdiffusion of bubbles and hyperoxygenation of compromised tissue. Treatment in a recompression chamber is mandatory for these disorders. Carbon monoxide poisoning results in noncompetitive binding of carbon monoxide with hemoglobin and myoglobin and reversible binding to the cytochrome system. HBO reverses hypoxia, displaces CO from the heme proteins (hemoglobin, myoglobin, cytochrome system), prevents WBC adherence to endothelium, and reduces lipid peroxidation in the central nervous system. Candidates for therapy include those with mental aberration, cardiac ischemia, or a history of unconsciousness and coma, particularly if hypotension has been present. Treatment within 6 hours of exposure has yielded the best results.

Gas gangrene is caused by necrotizing toxins released by pathologic clostridial organisms. Bacterial growth may be severely restricted by tissue oxygen levels of 70 mmHg; tensions of 250 mmHg halt alpha-toxin production. Organisms other than *Clostridia* can also cause necrotizing infections. These are generally synergistic combinations of bacteria with differing oxygen requirements. HBO can serve as a useful adjunct to definitive surgical and antibiotic treatment, often preventing the need for amputation or ablative surgery.

Crush injury involves severe trauma to bones, soft tissue, nerves, and vascular structures and often results in marginal oxygenation of peripheral tissue. In this setting, HBO should be initiated as soon as possible to enhance support of marginally viable tissue, leukocyte killing, and edema reduction. A reduction in surgery and improved salvage have been demonstrated, particularly in patients aged more than 40 years.

In chronic refractory osteomyelitis, periodic elevation of bone O_2 levels from hypoxic to normal or above-normal levels promotes fibroblast division, collagen production, capillary angiogenesis, increased leukocyte killing, and osteoclast activity. HBO must be used as an adjunct to surgical debridement, wound care, and appropriate long-term antibiotic administration.

Radiation necrosis, soft-tissue radiation injury, and osteoradionecrosis share a common pathophysiology of obliterative endarteritis, secondary tissue ischemia, and hypoxia. Daily HBO can restore a functioning capillary bed and facilitate surgical intervention, if necessary. Surgery in previously irradiated tissue is otherwise associated with a high incidence of potentially fatal complications. HBO also is indicated postoperatively to ensure adequate capillarity for healing.

Hyperbaric oxygen therapy is not indicated for normal skin flaps, grafts, or surgical wounds. It can be used for preparing a granulating base for skin grafting where viability of a graft or flap is compromised or uncertain or when previous grafts have failed. Preoperative HBO therapy is effective in promoting capillary proliferation to prepare a site in poorly granulating wounds. In selected problem wounds (e.g., diabetic ulcers, chronic nonhealing wounds), HBO therapy can be used as an adjunct in a regimen of meticulous wound care, careful attention to nutritional status, metabolic control, and revascularization, when indicated.

Adjunctive HBO for thermal injury is controversial. Some burn centers experienced in its use have reported reductions in length of hospital stay, need for grafting, and mortality rates. HBO should be restricted to facilities associated with a burn center.

Recent data suggest that HBO may have a potent effect on ischemia reperfusion injury. This effect appears to be mediated by nitric oxide (NO) providing temporary but reversible blocking of the CD11/CD18 integrins and their binding with endothelial cellular adhesion molecules. High doses of oxygen appear to have a profound effect on this reaction, ameliorating many of the effects of reperfusion injury by increasing NO synthesis.

The importance of NO in the wound healing process is becoming increasingly appreciated. Several investigators have also demonstrated that HBO serves as a signal transducer for the production of growth factors such as platelet-derived beta and vascular endothelial growth factor, both of which are necessary for tissue repair. Many of these reactions appear to be mediated by a direct effect of HBO at the gene level. As an understanding of these processes improves, the prescription of HBO therapy may become more precise.

Risks involved in the use of HBO therapy are related to pressure changes and the toxic effects of oxygen. They include barotrauma to the ears or sinuses, pulmonary overpressure accidents with pneumothorax, and pulmonary toxicity. Trauma to the ears or sinuses can be averted with slow compression, the use of decongestants, and patient education. Occasionally myringotomy is necessary. Pulmonary overpressure accidents are rare, perhaps 1 in 50,000 treatments, and can be avoided by careful pretreatment screening for pulmonary blebs, air trapping caused by bronchospasm or secretions, and the presence of preexisting pneumothorax secondary to chest compression, central lines, ventilatory support, or other forms of trauma. An undetected pneumothorax at sea level can be converted to a tension pneumothorax on ascent as ambient pressure decreases. Treatment is immediate insertion of a chest tube, which will allow the hyperbaric treatment to continue if warranted.

Oxygen itself has definite toxic effects as a result of overdosage, usually affecting the brain or lungs. Exposure to oxygen at depth can cause grand mal seizures, possibly related to interference with gamma-aminobutyric acid metabolism. Susceptibility varies widely. As the (PO_2 value rises, so does the risk of seizures. For this reason, oxygen treatments are limited to a maximum depth of 3 ATA (atmosphere absolute), or 66 ft of sea water, 20 m. Fever and certain medications can predispose to this complication, and careful attention to potential drug enhancement is mandatory. Oxygen seizures, in fact, are rare, perhaps occurring in 1 of 10,000 to 12,000 treatments. They are self-limited and treated by cessation of oxygen therapy. HBO treatment can be reestablished after seizure activity has ceased. Patients should be checked for any underlying pathology.

Damage to lung tissue, manifested by a decrement in vital capacity and irritation to the large airways, is a predictable complication of oxygen exposure at depth. The mechanism is believed to be loss of surfactant and changes in the pulmonary macrophages. Because toxicity is related to the depth and duration of exposure, treatment protocols are designed to use the shallowest depth consistent with the desired results. In practice, pulmonary toxicity from currently used wound healing protocols is virtually unheard of. Additional minor side effects are a change in visual acuity that reverts to baseline within a few weeks to months after treatment. No evidence indicates that protocols presently used in the United States predispose to cataract formation.

Although not a complication of treatment, confinement anxiety can be a problem for patients being treated in hyperbaric chambers. Sedation and reassurance usually remedy the problem. A small percentage of patients cannot tolerate treatment.

The ability to preserve a functional extremity can reduce the high cost of disability resulting from amputation. These effects appear to be durable. The shortened healing time for chronic wounds will reduce the cost of frequent, repeated surgical procedures. Most important, however, is the reduction in morbidity associated with acute and chronic tissue injury. Reversal of local ischemia with HBO appears to be a new and useful application of this treatment in selected cases.

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III. PULMONARY INFECTION

21. THE LUNG IN DRUG ABUSE

Robert J. Kruklitis and Charles A. Read

Drug abuse and its protean medical complications account for significant morbidity and mortality, worldwide. The lungs are particularly vulnerable to these agents because the most common routes of drug administration are inhalation and intravenous. Pulmonary complications can be classified generally as infectious and noninfectious (Table 21.1). An understanding of these complications and their typical presentation is essential for the proper diagnosis and treatment among drug-abusing patients.

Illicit drug abusers are susceptible to numerous infectious complications. These complications arise secondary to depression of the host's immune defenses or from inadvertent inoculation with infectious agents such as the human immunodeficiency virus (HIV). Many pulmonary complications are related to HIV infection, such as pneumocystic pneumonia, tuberculosis, and Kaposi's sarcoma, to name a few. The pulmonary manifestations of HIV infection are reviewed elsewhere (Chapter 44). The mechanisms involved in drug-induced immune suppression remain to be elucidated. Recent studies in cocaine and marijuana users document impairment in the function of alveolar macrophages. Exposed macrophages cause both reduced phagocytosis and bacterial cell killing. Additionally, impairment occurs in the production of various inflammatory cytokines, including TNF-α and IL-6, by the macrophages of marijuana smokers. These findings may begin to explain the enhanced susceptibility to infections that occurs in drug addicts.

Aspiration into the tracheobronchial tree is common in drug-abusing patients. This occurs independent of the administration route or class of illicit drug. After an overdose, which often causes a stuporous or comatose state, risk of aspiration is increased because of central nervous system depression and absent or reduced cough reflex. Either a pneumonitis or pneumonia can result from the aspiration of oropharyngeal and gastric contents. The initial inflammatory response can result in significant alveolar edema. Patients often become tachypneic, hypoxic, and febrile. Radiographically, is seen a range from normal to bilateral diffuse infiltrates, depending on the amount of aspirate and degree of resulting inflammation. Treatment is generally supportive. The use of antibiotics after an episode of aspiration is controversial but should be guided by the clinical situation. If used, antimicrobial therapy should be directed primarily against the oral flora.

Septic pulmonary emboli are also common in injection drug users. One study documented septic emboli in nearly one quarter of the hospitalized drug addicts with pulmonary complaints. Emboli originate from either endocarditis, typically of the tricuspid valve, or from thrombophelebitis at the injection site. Presenting symptoms typically include pleuritic chest pain, hemoptysis, and fever. Physical examination in the case of thrombophelebitis reveals redness, induration, and warmth at the injection site. A palpable cord may or may not be present. In contrast, endocarditis of the tricuspid valve can be difficult to detect on examination. Tricuspid murmurs are often soft and the peripheral stigmata of endocarditis are not present with right-sided lesions. Typical radiographic manifestations include diffuse, sequentially appearing round or wedge-shaped peripheral infiltrates, which may or may not cavitate. Often is seen hilar and mediastinal lymphadenopathy and, occasionally, a coexistent pleural effusion. *Staphylococcus aureus* occurs most frequently; however, gram-negative bacteria and *Candida* are also potential pathogens. Appropriate antimicrobial therapy is typically effective at alleviating symptoms and resolving the infiltrates if compliance can be achieved.

Community-acquired pneumonia occurs at an increased frequency in the drug-abusing population. It has been estimated that drug abusers have a 10 times higher incidence of community-acquired *Streptococcal pneumoniae* pneumonia compared with nondrug users. Additionally, as previously discussed, drug abusers develop aspi-

Table 21.1. Pulmonary complications of illicit substance abuse

Infectious
–Aspiration pneumonia
–Septic emboli
–Bacterial pneumonia
–Acute bronchitis
–Tuberculosis
–Fungal pneumonia
Noninfectious
–Vascular complications
—Noncardiogenic pulmonary edema
—Pulmonary hemorrhage
—Pulmonary hypertension
–Interstitial complications
—Talc granulomas
—Pulmonary fibrosis
–Airway complications
—Bronchospasm/asthma
—Chronic bronchitis
—Bullous disease
—Bronchiectasis
—BOOP (bronchiolitis obliterans with organizing pneumonia)
–Pleural complications
—Pneumothorax/pneumomediastinum
—Pleural effusions/empyema
–Ventilatory failure
–Carcinogenesis

ration pneumonia and can acquire pneumonia hematogenously from septic emboli. As many as 30% of the drug abusers presenting with fever have pneumonia. Pneumonia in drug abusers behaves as it does in the non–drug-using population. The history, physical examination, range and frequency of offending organisms, severity of disease, and outcome with conventional therapy are all equivalent in both drug users and nonusers. If inadequately treated, pneumonia can result in several severe complications such as lung abscess, empyema, and adult respiratory distress syndrome (ARDS). These complications require aggressive conventional therapy.

Acute bronchitis similarly develops at an increased frequency in marijuana users. This increased incidence is felt to result, in part, from the high content of respiratory irritants in marijuana smoke. Although not well studied, other inhalational drugs might also predispose their users to acute bronchitis. The treatment of acute bronchitis in drug abusers is equivalent to that in nonabusers.

Pulmonary tuberculosis also arises more frequently in drug abusers than in nonusers. Although this may, in part, be due to a lower socioeconomic status, this alone does not explain the increased incidence of tuberculosis. Other factors, such as a depressed immunity in addicts, contribute to the higher rate of reactivation in this population. Clinically and radiographically, tuberculosis is indistinguishable in drug abusers and nonusers. Tuberculosis should be treated with the standard multiple antimycobacterial agents in both groups. Directly observed therapy is advisable in all drug addicts in order to ensure compliance.

Fungal pulmonary infections have rarely been linked to illicit substance use. Cases of fulminant invasive aspergillosis have been reported in immunocompromised patients who smoked marijuana that was contaminated with the fungus. Additionally, smoking aspergillus-laden marijuana has resulted in allergic bronchopulmonary aspergillosis,

presumably by promoting colonization of the lower respiratory tract. Candidal pulmonary infections are also felt to have occurred from contaminated drugs. Sliced lemon, which is used to acidify the heroin fix, is the likely source of candidal contamination. Heroin use has resulted in lobar candidal pneumonia as well as systemic candidiasis with ARDS. Although these severe fungal infections are rare, drug abusers have a high prevalence of serum precipitins against these fungi. This suggests widespread fungal contamination of illicit drugs. Treatment should focus on standard aggressive antifungal therapy.

Illicit substance abuse is also responsible for numerous noninfectious complications. These complications can be categorized according to anatomic location as follows: the pulmonary vasculature, interstitium, airways, and pleura. Three serious, potentially life-threatening, conditions involve the pulmonary vasculature: noncardiogenic pulmonary edema, pulmonary hemorrhage, and pulmonary hypertension.

Noncardiogenic pulmonary edema is perhaps the most frequent fatal complication of illicit drug abuse. In one large series, 18% of those with heroin-induced pulmonary edema died. Most drug classes, including narcotics, cocaine, amphetamines, sedatives, tranquilizers, analgesics, and hydrocarbons, can acutely produce pulmonary edema, but heroin is a particularly common offender. Pulmonary edema, which has been documented in the first-time user and with the experienced addict, can occur immediately or up to 24 hours after use. Patients typically appear quite ill, are hypoxic and have pulmonary rales. They are often stuporous or may be comatose. Roentgenography classically demonstrates fluffy bilateral alveolar infiltrates without cardiomegally. Although the precise pathophysiology remains unknown, and can be different among the various drug classes, an increase in capillary permeability appears to occur, as the protein concentration of the edema is nearly equivalent to that of serum. Treatment is generally supportive with supplemental oxygen and mechanical ventilation as needed. Naloxone should be considered in opiate-induced edema as it might reverse respiratory depression. Typically, the edema will resolve spontaneously within 24 to 72 hours, but it can take several weeks until the lung volumes, compliance, and diffusing capacity normalize.

Crack lung is a syndrome that includes fever, cough, wheezing, hypoxemia, diffuse alveolar infiltrates, and eosinophilia in both peripheral blood and in bronchial alveolar lavage washings. This constellation of findings can develop immediately, or up to 48 hours after smoking crack cocaine. Typically, the infiltrates will resolve spontaneously. Corticosteroids, which have also been used, have resulted in mixed success. Whether crack lung is a distinct entity or is part of the spectrum of noncardiogenic pulmonary edema, remains unclear.

Pulmonary hemorrhage has typically been described in the users of inhaled free-base cocaine. Other drugs are less likely to cause hemoptysis; however, volatile hydrocarbons and heroin have been associated with at least subclinical pulmonary vascular hemorrhage. Hemorrhage can be either occult, with up to one third of cocaine-using patients having hemosiderin-laden macrophages in their lungs at autopsy, or massive, which requires emergent lobectomy. Although massive hemoptysis is rare, users of free-base cocaine frequently report black or blood-tinged sputum after use. It has been postulated that pulmonary hemorrhage occurs from either the intense vasoconstriction caused by cocaine or from direct alveolar injury. Chest radiographs are usually normal and unrevealing. Treatment, as with other forms of hemoptysis, depends on its extent but is mainly supportive. Bronchoscopy is indicated with significant hemoptysis in order to locate the origin of the bleeding.

Pulmonary hypertension can also result from intravenous (IV) substance abuse. Pulmonary hypertension occurs secondary to the embolization of foreign particles into the pulmonary vasculature. Addicts often prepare and inject suspensions of tablets containing insoluble filler components (e.g., talc, cellulose, or cornstarch). The most frequently crushed and injected tablets include amphetamines, methylphenidate (Ritalin), methadone, and propoxyphene (Darvon). Other drugs, such as heroin, are cut with these insoluble particles or have them added as adulterants. Over time, repeated embolization of these particles results in thrombosis, fibrosis, and ultimately pulmonary vessel occlusion. Progressive loss of the pulmonary microcirculation eventually leads to pulmonary hypertension and, if untreated, to cor pulmonale. Treatment

options are limited, with the best therapy being cessation of IV drug use and, thus, embolization. Empirical prednisone therapy has resulted in mild improvement in the signs and symptoms of pulmonary hypertension in some patients.

Interstitial lung disease, in the form of pulmonary fibrosis and granulomatosis, can also result from the embolization of insoluble particles. Embolized foreign bodies cause endothelial injury in the pulmonary vasculature. Initially, a focal inflammatory process develops that leads to damage of the arterial walls. Ultimately, transvascular migration of the insoluble particles occurs with the formation of perivascular and interstitial granulomas. Patients will complain of progressive exertional dyspnea, mild cough, and, occasionally, wheezing. Fundoscopic examination often reveals glistening white spots around the macula. Chest radiography may be normal or may have diffuse reticulonodular infiltrates most prominent at the lung bases. Hilar and mediastinal adenopathy is occasionally observed. This occurs because these impurities are filtered by the lymphatics and, thus, can lead to lymphoid hyperplasia. Patients classically have a decreased diffusion capacity and an obstructive pattern on pulmonary function testing; however, a restrictive pattern may also be seen. Definitive diagnosis requires that either a transbronchial or open lung biopsy demonstrate foreign body granulomas containing birefringent talc or other foreign particle. Anecdotal evidence suggests that steroids may be of mild benefit in some patients. Unfortunately, other studies document progressive worsening respiratory status despite discontinuation of drug use.

Tracheal stenosis has been reported with smoking crack cocaine. The extremely high temperatures achieved in the inhalant place users at risk for developing tracheal stenosis from a burn injury. Reactive airway disease can also occur in their proximal airways. Patients will present with bronchospasm, which may be irreversible, and occasionally with stridor. Severe tracheal stenosis may require a mechanical correction, including tracheostomy placement.

Bronchospasm can occur after the use a variety of inhalational drugs, with cocaine and narcotics being frequent offenders. The drugs themselves, or their adulterants, result in inflammation of the respiratory epithelium. Additionally, these drugs cause the release of histamine that worsens the bronchospasm. Avoidance of the precipitating drugs, along with conventional bronchodilator therapy, is the treatment of choice. Exacerbation of asthma is responsible for significant morbidity and occasional mortality in the drug-abusing population.

Chronic bronchitis and impaired gas exchange occur with the repeated use of marijuana. Initially, marijuana causes bronchodilation and was once assessed as a possible therapy for asthma. Bronchodilation results from a mechanism that is independent of antimuscarinic or beta-agonistic activity. Unfortunately, these bronchodilatory effects are only transient. In contrast, chronic use of marijuana results in a significant decrease in diffusion capacity and probably mild airflow obstruction. Furthermore, regular users develop irritation and inflammation of their airways that is characteristic of chronic bronchitis.

Obstructive lung disease can also result from damage to the medium and small airways. *Bronchiectasis* has been reported in drug users after one or more episodes of noncardiogenic pulmonary edema. Aspiration, hypoxia, and direct irritant effects can all contribute to the development of bronchiectasis. Cocaine users are at risk of developing *bronchiolitis obliterans with organizing pneumonia*. Typically, these patients are improved with steroids, but several cases of ARDS and ultimately death have occurred. The best available long-term therapy for brochiectasis and bronchiolitis obliterans is cessation of drug use, as repeated exposure generally leads to worsening of the disease.

Bullous lung disease occurs occasionally in the users of IV drugs—up to 2% in one large retrospective study. Bullous disease, which is predominately located in the upper lobes, occurs much earlier than expected from cigarette smoking alone. The pathophysiology of bullae formation is uncertain. It is speculated that bullae result from the coalescence of microbullae, which are formed indirectly from either emboli or foreign body granulomas. Patients present with obstructive symptoms analogous to those in patients with moderate to severe emphysema.

A *pneumothorax* or *pneumomediastinum* can result from the use of either intravenous or inhalational drugs. As sites for peripheral access are exhausted, IV drug abusers often attempt to access the subclavian and internal jugular venous systems.

A *pocket shot*, which is an injection lateral to the sternocleidomastoid muscle immediately above the clavicle, is a common practice. Complications of pneumothorax, pneumomediastinum, pseudoaneurysm formation, and paralysis of the vocal cord caused by recurrent laryngeal nerve trauma have all been reported. Pneumomediastinum and pneumothorax formation can also be seen with inhalational drug use. This occurs either because of weakness and chronic inflammation of the alveolar walls or from an increased pressure gradient. The latter can be seen with an increased alveolar pressure, which is generated by performing a Valsalva's maneuver after inhalation, or from decreased interstitial pressure caused by vasoconstriction, particularly with cocaine and amphetamines.

Ventilatory failure, caused by suppression of the respiratory drive, occurs with several different drug classes. Narcotics and sedatives especially predispose to suppressing ventilation; their use can result in carbon dioxide retention, decreased consciousness, ventilatory failure, and, ultimately, death. Treatment includes the use of naloxone and flumazenil in the hope of antagonizing these drugs and, thereby, reversing the respiratory depression. Mechanical ventilation may also be required to overcome the ventilatory failure. The recent popularity of ketamine and gamma hydroxy butyrate has added analgesics to the list of illicit drugs capable of causing death by respiratory depression.

Lung cancer occurs with increased frequency in tobacco smokers. At present, information is scarce regarding the incidence of bronchogenic carcinoma in the users of illicit drugs. Evidence, however, suggests that marijuana and cocaine smoking may be carcinogenic. Specifically, both histological and molecular alterations in the bronchial epithelium have been identified in the smokers of cocaine and marijuana. Similar alterations are seen in tobacco smokers. Although not studied, other illicit substances may have similar carcinogenic effects. Cessation of drug use is obviously essential in these patients.

The pulmonary manifestations of illicit substance abuse, which can be divided into infectious and noninfectious, are diverse and present with a wide range of signs and symptoms. Some complications occur acutely (e.g., pulmonary edema or aspiration pneumonia), whereas others (e.g., pulmonary fibrosis and hypertension) require repeated and chronic drug use. Some can be immediately life threatening, as is the case with pulmonary edema or ventilatory failure, and most are serious and disabling. Performing a complete history and physical examination is the first step toward obtaining an accurate diagnosis. A high index of suspicion in addition to a thorough history with regard to drug use is essential. Neglecting to do this can result in needless tests, inaccurate diagnosis, and inappropriate treatment. Unfortunately, the true magnitude of this problem is unknown, partly because of the difficulty of definitively proving that a pulmonary process is the direct result of drug use. Most medical literature contains isolated reports or case series on a particular complication of illicit drug use. A distinct absence is seen of studies aimed at determining optimal therapy for these complications. Obviously, every attempt to promote discontinuation of drug use should be made. Otherwise, therapy is generally supportive and parallels that used to treat nondrug abusers with similar problems.

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22. PNEUMONIA: GENERAL CONSIDERATIONS

Gordon L. Yung

Pneumonia is defined as infection of the lower respiratory tract parenchyma by agents such as bacteria, viruses, fungi, or even parasites. It should be distinguished from *pneumonitis*, which is an inflammation of the lungs from a variety of noninfectious causes including chemicals, blood, radiation, and autoimmune processes. Pneumonia, the sixth leading cause of death in the United States, is responsible for approximately 4 to 10 million respiratory tract infections each year. Microbial agents can be introduced to the lungs via several routes, including (a) aspiration of oropharyngeal secretions; (b) inhalation; (c) hematogenous spread via the pulmonary or bronchial circulation; and (d) less commonly, direct spread from surrounding structures. The occurrence and severity of pneumonia depends on both the state of the body's defense mechanisms against infection and on the size and virulence of the microbial inoculum itself. A review of the complex interaction between these factors is helpful in understanding the pathogenesis of pneumonia and in creating effective diagnostic and treatment strategies.

The most common mechanism triggering pneumonia is upper airway colonization by potentially pathogenic organisms, which are subsequently aspirated. The type of organism involved depends, in part, on host characteristics. Virulent organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* can transiently colonize healthy individuals. *Staphylococcus aureus* and *Pseudomonas* species can be isolated in upper airways of hospitalized patients. Mixed anaerobic flora are usually of low

virulence, but the massive quantities generated in the gingivodental recesses of those with poor dental hygiene predispose to anaerobic pneumonia. Although some degree of aspiration occurs in up to 45% of healthy adults at night, the normal body defenses (e.g., cough and continuous mucociliary clearance) usually prevent infection from developing. These defenses are compromised in intubated or debilitated patients, and in those with altered consciousness or those who aspirate large amounts of oropharyngeal contents.

Legionella species, mycobacteria, endemic fungi, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and most viral infections are examples of pneumonia resulting from direct inhalation of organisms. Direct inhalation of airborne droplets accounts, in part, for the geographic and seasonal clustering of cases caused by these organisms.

Less commonly, pneumonia can arise through hematogenous or embolic spread of infection. The pulmonary circulation acts as a filter for venous blood which, in some cases, allows microorganisms to lodge in the small vessels of the lungs and cause parenchymal infection. In most cases, the infections originate from infected heart valves or from thrombophlebitis. Because bacteria are released in clusters from the source, they are likely to reach multiple parts of the pulmonary circulation simultaneously, causing dense infections that can cavitate. Hematogenous pneumonias, therefore, are often multifocal, peripheral lesions that are susceptible to rapid cavitation.

Patients with pneumonia typically present with acute onset of cough, sputum production, fever, and dyspnea; some may also have pleuritic chest pain or hemoptysis. The symptoms, however, are nonspecific; noninfectious causes such as malignancy, pulmonary hemorrhage, and drug-induced pneumonitis can present similarly. Certain clinical and radiographic features may suggest specific organisms as the cause of pneumonia, as discussed in subsequent chapters. In practice, however, these features are often nonspecific and empirical treatment is usually necessary before a definitive diagnosis is made.

The initial antibiotic choice may be guided by Gram's stain of respiratory secretions. This requires the demonstration of a satisfactory sputum sample (defined as >25 polymorphonuclear leukocytes and <10 epithelial cells in each low power field) and the presence of a predominant organism (>8–10 organisms per high power field), particularly if the same bacteria are found within white blood cells. The presence of inflammatory cells without identifiable organisms should alert physicians to noninfectious causes of pneumonitis, as well as to *atypical* pathogens such as viruses, *Mycoplasma pneumoniae*, *Legionella* species, and *Chlamydia* species. A more definitive identification of organisms and their sensitivity to antibiotics is often necessary if patients do not respond to initial treatments.

Expectorated sputum is obtained in most cases, although its clinical utility has been debated for decades. This method of sampling is noninvasive but the yield is decreased if antibiotics are given before sample collection. In addition, conventional culture techniques of sputum samples will not detect *atypical* organisms. Finally, up to 30% of patients with pneumonia have a nonproductive cough. Although induced sputum is often obtained, its role has only been validated in pneumonia caused by tuberculosis or *Pneumocystis carinii*. For intubated patients, a negative Gram's stain and culture of endotracheal aspiration is a sensitive method to rule out pneumonia (provided antibiotics were not started before sampling). Interpretation of a positive endotracheal aspirate, however, is more difficult because of frequent contamination of the endotracheal tube and upper airways in intubated patients.

Despite extensive laboratory testing, a causative organism can be identified in only approximately 50% of all pneumonia cases. Many patients, particularly those hospitalized and on ventilator support, may also have conditions that mimic pneumonia (e.g., atelectasis, pulmonary embolism, and vasculitis). Invasive tests are sometimes used in selective cases to improve diagnostic yield.

Flexible bronchoscopy is probably the most common invasive procedure used to diagnose pneumonia. It can be useful in patients who are unable to produce a satisfactory sputum sample. It allows direct sampling of distal airway secretions from selective bronchial segments that correspond to the changes on chest radiographs. Samples are obtained either by simple washing of a bronchial segment or by bronchial alveolar lavage (BAL). Because of potential contamination while passing through upper air-

ways, a protected brush specimen (PBS) is sometimes obtained. In most bacterial pneumonias, unfortunately, samples obtained by flexible bronchoscopy do not provide more diagnostic accuracy than expectorated sputum. Some investigators contend that a semiquantitative culture by bronchoscopy, defined as PBS more than 10^3 or BAL more than 10^4 or 10^5 colony forming units/ml, may improve the diagnostic yield of bronchoscopy. One meta-analysis showed a sensitivity of 91% and a specificity of 95% for PBS, whereas BAL had a sensitivity of 86% to 100% and a specificity of 100%. These results may be affected by prior antibiotic administration, operator skill, and laboratory support. Currently, routine use of PBS or BAL is not recommended when bacterial pneumonia is suspected. However, bronchoscopy may be helpful in identifying infection under several conditions: (a) *P. carinii* in patients with the acquired immunodeficiency syndrome; (b) cytomegalovirus in posttransplant patients; and (c) tuberculosis or other granulomatous lung infections when with a strong clinical suspicion despite negative findings on expectorated sputum. In addition, bronchoscopy allows sampling for opportunistic organisms in immunocompromised patients, as well as direct visualization of airways, when bronchial obstruction is suspected. Transbronchial biopsy may provide tissue evidence of invasion by microorganisms (e.g., *Aspergillus* sp.), distinguishing between colonization and invasive disease. It has also been used to diagnose noninfectious causes of pneumonitis.

Other invasive techniques have been used to bypass the upper airways. Percutaneous transthoracic lung aspiration, with or without the use of fluoroscopy, uses a small bore needle to aspirate approximately 0.5 to 2 ml of lung tissue sample. The technique appears to increase the diagnostic yield of pneumonia when combined with blood culture results; but, similarly to other techniques, it is insensitive in patients who have received prior antibiotics. It is useful in cases where masslike lesions are present and, because contamination is less likely, it provides valuable information in cases where multiple organisms are involved. Pneumothorax can complicate the procedure, especially in the setting of chronic lung disease. Transtracheal aspiration was used extensively in the 1970s, primarily for the diagnosis of anaerobic infections, and in immunocompromised patients. Because of the adverse effects of these *minimally invasive* techniques, they have been largely replaced by flexible bronchoscopy. Finally, open lung biopsy, by minithoracotomy or thoracoscopy, can provide adequate tissue for histologic examination but the risks and discomfort of the procedure limit its clinical usefulness. It is only used in cases of *unresolved pneumonia*, where a noninfectious cause is suspected.

Recently, several guidelines have been developed to provide a systematic approach to the management of pneumonia. Two questions should be asked in the initial evaluation of pneumonia: (a) Is the pneumonia community acquired or hospital acquired? (b) What are the risk factors to the development of pneumonia?

Community-acquired pneumonia occurs twice as frequently during winter; and people at the extremes of age (<5 years and > 65 years) are at increased risk. *S. pneumoniae*, the most common causative agent, is responsible for about half of all cases. Other common causes include *M. pneumoniae*, *C. pneumoniae*, and *H. influenzae*. Patients with comorbid conditions or those aged more than 65 years are also at risk of pneumonia from *Legionella* species, *S. aureus*, and gram-negative organisms. The decision to admit a patient to the hospital for treatment should take into consideration the known risk factors for increased mortality from pneumonia. These include (a) age more than 65 years; (b) comorbidities such as diabetes mellitus, renal or congestive heart failure; (c) altered mental status; (d) tachycardia (>125 beats/min); (e) tachypnea (>30/min); (f) high fever (>38.3° to 40°C); (g) hypotension (systolic blood pressure < 90 mm Hg); (h) hypoxia (SaO_2 < 90% or PaO_2 < 60 mm Hg); (i) multilobar involvement on chest radiograph; and (j) identification of *high-risk* pathogens such as gram-negative organisms and *S. aureus*. When appropriate, outpatient management of community-acquired pneumonia should include a chest radiograph and complete blood count. The role of routine sputum and blood cultures in this setting is controversial. The recommended treatment for community-acquired pneumonia is a course (7–10 days) of a macrolide (erythromycin, clarithromycin, or azithromycin); an extended spectrum fluoroquinolone (levofloxacin, sparfloxacin or grepafloxacin); or doxycycline.

The choice of treatment should also be influenced by local antibiotic resistance patterns. In-patient management of community-acquired pneumonia should include sputum Gram's stain and culture, as well as blood culture. For hospitalized patients,

initial therapy for community-acquired pneumonia usually includes a cephalosporin such as ceftriaxone or cefuroxime, with or without a macrolide. Antibiotic treatment should be given as soon as possible, because mortality can increase even after a short delay (>8 hours) in receiving appropriate antibiotics.

Hospital-acquired pneumonia, also termed *nosocomial pneumonia*, is the second most common infection in hospitalized patients and the most common infection in the intensive care unit. Intubated patients are 6 to 21 times more likely to develop pneumonia and the incidence increases with the duration of intubation and poor infection control practices. In the first 5 days of hospitalizations, *H. influenzae*, *S. pneumoniae*, and *S. aureus* are often isolated. After this time, pneumonia is often caused by *P. aeruginosa*, *S. aureus*, anaerobic microbes, *Acinetobacter* species, and various gram-negative enteric bacilli. Unlike community-acquired pneumonia, mixed flora and resistant organisms are commonly isolated, a finding with important therapeutic implications. Initial therapy depends on factors such as the length of hospital stay, severity of pneumonia, risk of aspiration, and other comorbidities. The management of hospital-acquired pneumonia is reviewed in a subsequent chapter.

Empiric therapy is often required for pneumonia, and identification of specific clinical risk factors may help tailor the initial management. Patients with acquired immune deficiency syndrome or those immunosuppressed from chemotherapy or post-organ or bone marrow transplantation have increased risk of developing pneumonia from a wide variety of bacteria, viruses, fungi, and even parasites. Encapsulated organisms such as *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis* commonly cause pneumonia in patients with hypogammaglobulinemia or after splenectomy. In addition, neutropenic patients are more susceptible to infection by gram-negative bacilli and *Aspergillus* species. Anaerobic infections should be considered in patients with aspiration risks, whereas patients with recent influenza infection are at risk of developing pneumococcal and *S. aureus* pneumonia. Because of the high incidence of pneumonia by some organisms in immunocompromised patients, prophylactic therapy is increasingly being used, with promising results. Typical examples are the use of trimethoprim–sulfamethoxazole to prevent *P. carinii* pneumonia in patients with the human immunodeficiency virus disease, and ganciclovir in cytomegalovirus-mismatched transplant recipients.

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23. PNEUMOCOCCAL PNEUMONIA

Julian P. Lichter

Pneumococcal pneumonia is the most common infection leading to hospitalization in the United States. It occurs in all age groups and is responsible for 500,000 cases of pneumonia and approximately 40,000 deaths annually. Pneumococcal pneumonia accounts for more than 50% of community-acquired pneumonias and 10% of nosocomial pneumonias. Outbreaks of pneumococcal pneumonia have occurred in chronic care facilities, particularly those involving antibiotic resistant strains. Although pneumococcal pneumonia can occur in any season, it is more common in winter and early spring.

The pneumococcus frequently inhabits the nasopharynx of normal individuals. The probability and severity of infection are influenced by host factors and by the biologic properties of the bacterium itself. Patients who are most susceptible to pneumococcal infection include those with (a) disorders of swallowing, coughing, and impairment of airway clearance mechanisms and mucociliary defenses (advanced age, chest trauma, seizure disorder, neurologic disorder, chronic bronchitis, bronchiectasis); (b) alveolar fluid accumulation (congestive heart failure, burns, acute respiratory distress syndrome); and (c) impaired phagocytosis, and compromised humoral immunity (surgical or functional asplenia (i.e., sickle cell anemia, hypogammaglobulinemia, diabetes, acquired immunodeficiency syndrome, multiple myeloma, lymphoma, cirrhosis). Such individuals are also susceptible to protracted or complicated pneumonias. Viral upper respiratory illness also seems to predispose patients to subsequent pneumococcal pneumonia. Viral disruption of respiratory epithelium increases expression of receptors for pneumococcal attachment and, thus, predisposes the patient to pneumococcal invasion.

Of the more than 82 strains of pneumococci, only a few commonly cause pneumonia. The pathogenicity and virulence of particular strains are related to properties of the outer capsules and cell walls, as well as surface and cytoplasmic regulatory mechanisms. They may be identified in the laboratory by a characteristic capsular *swelling* (quellung reaction) when incubated with specific antibody. Current evidence suggests that the pneumococcal capsule protects the organism from phagocytosis and enhances its pathogenicity. Recent studies suggest that the development of type-specific, anticapsular antibody correlates with the resolution of fever and recovery in untreated patients.

Pneumococci are aerosolized from the nasopharynx to the alveolus, and then pass from alveolus to alveolus through the pores of Cohn, resulting in a mostly lobar distribution of consolidation. They invade alveolar type II cells, a process initiated through binding of bacterial surface choline to the receptor for platelet-activating factor (upregulated on the alveolar cell surface, presumably, by viral infection). Pneumococci produce a potent cytotoxin, pneumolysin, which binds to cholesterol on the host's cell membranes, forming pores and killing the cells. Pneumolysin also promotes intraalveolar bacterial replication, penetration from alveoli to interstitium, and dissemination into the bloodstream. Approximately 25% of cases of pneumococcal pneumonia have associated bacteremia.

The clinical manifestations of classic pneumococcal pneumonia include high fever (100% in one series, although high fever may be absent in the elderly or in uremic patients), productive cough (98%), pleuritic chest pain (70%), and the abrupt onset of shaking chills (7%). The sputum is blood streaked or *rusty* (75%). Pleuritic pain may radiate into the abdomen, masquerading as an acute abdomen. The individual characteristically appears acutely ill and tachypneic, with signs of consolidation apparent on chest examination; a pleural rub is occasionally present. Herpes labialis is a relatively common finding. The chest roentgenogram usually reveals a lobar, alveolar-filling process, frequently with an ipsilateral pleural effusion. The roentgenographic presentations, however, are diverse and include a patchy bronchopneumonia, adult respiratory distress syndrome, and an *interstitial* appearance when in an emphysematous lobe.

As with other bacterial pneumonias, the methods and criteria for establishing a diagnosis are controversial. Gram's stain of expectorated sputum typically reveals numerous polymorphonuclear granulocytes and lancet-shaped gram-positive diplococci. However, the predominant organism may not be obvious on some specimens because of heavy smear contamination with oropharyngeal flora. Sputum Gram's stain and culture also can be misleading in patients who have received prior antibiotics and in patients with chronic obstructive pulmonary disease. Isolation of the organism in the sputum is not sensitive for the presence of infection; in fact, only 45% of patients with pneumonia and blood cultures positive for pneumococci grow the organism on sputum culture. For this reason, many *culture-negative* cases of pneumonia may be caused by the pneumococcus. Furthermore, sputum Gram's stain and culture may be nonspecific and isolation of the organism from blood, pleural fluid, or other involved closed tissue space (e.g., joint, cerebrospinal fluid, pericardium) may be required for a firm diagnosis.

Much of our understanding of the natural history of pneumococcal pneumonia comes from experience during the *preantibiotic era*, when three clinical patterns were observed:

(a) a 5- to 10-day course characterized by high fevers with defervescence and recovery occurring either gradually (*lysis*) or dramatically (*crisis*); (b) a protracted or recrudescent febrile course indicative of complications such as empyema, meningitis, endocarditis, and pericarditis; or (c) rapid respiratory deterioration and death. An initial leukocytosis exceeding 20,000 correlated with a good prognosis, whereas a normal or low leukocyte count implied a grave prognosis. An abrupt fall in leukocyte count often preceded resolution by crisis, but persistent leukocytosis frequently was a harbinger of complications such as empyema.

Although antibiotics have improved survival, pneumococcal pneumonia remains a serious disease. In the preantibiotic era, the overall mortality rate was 25% to 35%. In bacteremic patients, it exceeded 80%. Antibiotics have reduced the mortality rate to 5% and 20%, respectively. Nevertheless, the mortality in bacteremic patients infected with type 3 pneumococcus currently remains at 51%. Of patients who die despite antibiotic therapy, 35% die within the first 24 hours of antibiotic treatment, underscoring the fulminant course this disease can pursue. Furthermore, the fact that survival curves for antibiotic-treated patients and untreated (preantibiotic era) patients fail to diverge until after 5 days of illness points to the important impact of host factors and organism virulence on the outcome of this disease. Mortality in those who require mechanical ventilation remains high. Advanced age, inability to mount a fever, and nosocomially acquired pneumococcal pneumonia are the greatest risk factors for respiratory failure or death.

Penicillin G continues to be the drug of choice for sensitive pneumococcal pneumonia. It is effective either orally or intramuscularly in moderately to severely ill patients, but should be administered intravenously in the critically ill and in those with empyema or extra-pulmonary foci of infection. In patients allergic to penicillin, erythromycin or cefazolin are suitable alternatives. Therapy of uncomplicated pneumonia should be continued for at least 3 to 5 days after defervescence. Tetracycline is no longer an appropriate drug because of the emergence of resistant organisms in recent years.

It is becoming more common to find pneumococci that have become resistant to penicillin, probably through alteration of cellular penicillin-binding proteins. Approximately 5% to 10% of pneumococcal strains in the United States show an intermediate resistance, indicated by a mean inhibitory concentration of 0.1 to 1.0 μg/ml. In some areas (e.g., Alaska), as many as 20% to 25% of the strains demonstrate such resistance. In this setting, increasing the penicillin dose to 12 to 18 million units per day may be effective, as would administration of cefotaxime, ceftriaxone, imipenem, or one of the newer fluoroquinolones once sensitivities have been confirmed. Highly resistant pneumococcal isolates (types 6, 9, 14, 19, and 23), with a mean inhibitory concentration of at least 2 μg/ml, are common in Spain (44%), Hungary (>50%), and South Africa but are also becoming more numerous in the United States. Multiresistant strains (resistant to penicillin, trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, erythromycin, and even second- and third-generation cephalosporins) have also been found in the United States. Vancomycin, newer fluoroquinolones (e.g., levofloxacin) or an alternative agent based on in vitro sensitivities should be used for strains with high level penicillin resistance or resistance to multiple antibiotics. Drug-resistant infections have been observed in certain institutional settings, particularly day-care centers, hospitals, and nursing homes. Situations where the clinician should consider infection with a resistant strain of pneumococcus include (a) recent travel to areas where resistant strains are endemic; (b) a slower then expected response to therapy; and (c) patients receiving long-term or recurrent antibiotics.

The response to antibiotic therapy is usually apparent. In one large study (358 patients), 71% of patients were afebrile within 5 days of therapy. A protracted febrile course may indicate antibiotic resistance but also can occur in individuals who are elderly, anemic, or alcoholic and in those whose disease is characterized by bacteremia, multilobar involvement, or leukopenia. A slow clinical response is frequently associated with delayed radiographic resolution. In one series of bacteremic patients, only 13% had complete roentgenographic clearing within 2 weeks. Of the others, 61% cleared by 6 weeks, 78% cleared by 10 weeks, and 100% cleared by 18 weeks. Conversely, the chest roentgenogram can appear worse or unchanged, despite clinical improvement with

antibiotics. Thus, slow radiographic resolutions do not indicate treatment failure in the face of clinical response.

Complications of pneumococcal pneumonia include necrotizing pneumonia, lung abscess, meningitis, endocarditis, septic arthritis, and pleural disease. Pleural complications are common, and most patients have pleuritic chest pain. A pleural friction rub has been reported in 17% of cases. Pleural effusions can be detected in nearly 60% of patients if repetitive lateral decubitus chest radiographs are obtained. Although the effusions usually are sterile (parapneumonic) exudates, the incidence of empyema is approximately 15%. Diagnostic thoracentesis is mandatory for all large effusions occurring with pneumococcal pneumonia. A pleural fluid pH less than 7.2 suggests that empyema, rather than uncomplicated parapneumonic effusion, is present. A pleural fluid pH less than 7.1 is even more highly associated with empyema and the need for immediate chest tube drainage. Conservative treatment with antibiotics is usually successful if the pH is greater than 7.3.

Parapneumonic effusions usually resolve spontaneously. However, if they are large or symptomatic, they can be managed easily by thoracentesis. Both parapneumonic effusions and empyemas can accumulate during antibiotic therapy. Generally, the patient with empyema usually appears ill, with a persistent or recrudescent fever and leukocytosis. The degree of pleural disease correlates well with the extent of the initial pneumonia. Early therapy decreases the incidence of empyema.

Pneumococcal vaccines are available, which include 23 purified capsular polysaccharide antigens chosen to represent 90% of the serotypes that cause invasive disease in the United States. Approximately half of pneumococcal pneumonia deaths could potentially be prevented through the use of the vaccine, giving it the highest mortality rate of any vaccine-preventable disease. A serotype prevalence study based on the Centers for Disease Control's pneumococcal surveillance system demonstrated a 57% overall protective effect of this vaccine against invasive disease. Many trials have shown failure to protect against nonbacteremic pneumonia, as well as to protect those at the highest risk for pneumococcal pneumonia. Studies have demonstrated vaccine efficacy, however, in the elderly and in patients with diabetes mellitus or chronic pulmonary disease. Pneumococcal vaccine can be administered concurrently with other vaccines. The antibody levels to most vaccine antigens remain elevated for at least 5 years in healthy adults. Vaccination is recommended for all persons aged more than 65 years; persons with chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, and cerebrospinal fluid leaks; patients in chronic care facilities; patients with HIV infection, malignancy, and chronic renal disease; those receiving immunosuppressive chemotherapy or corticosteroids; asplenic patients; and in patients following organ or bone marrow transplant. Routine revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not recommended. A single repeat vaccination is recommended for persons aged more than 2 years who are at highest risk for serious pneumococcal infection, provided that 5 years have elapsed since the first dose. Promising improvements to the pneumococcal vaccine are currently in development, with some formulations showing efficacy in children as young as aged 2 months.

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24. STREPTOCOCCAL AND STAPHYLOCOCCAL PNEUMONIAS

Deborah Ann Hoffman

Streptococci and *staphylococci* are human pathogens responsible for a wide spectrum of infections including community-acquired and nosocomial pneumonias. The emergence of penicillin-resistant strains of *Streptococcus pneumoniae* and methicillin-resistant strains of *Staphylococcus aureus* has had a significant impact on our approach to infection caused by these organisms over the last decade.

Streptococci are spherical gram-positive bacteria that grow in pairs or chains. The bacteria are classified according to (a) the pattern of hemolysis demonstrated when the organism is cultured on blood agar (alpha refers to partial hemolysis, beta refers

to complete hemolysis, and gamma refers to nonhemolytic strains); (b) antigenic composition (Lancefield group); (c) colony morphology; and (4) other biochemical reactions and genetic analyses.

Streptococcus pneumoniae or pneumococcus is an alpha hemolytic streptococcus that typically appears as diplococci on Gram's stain. It is the pathogen most commonly isolated in hospitalized patients with community-acquired pneumonia (CAP), accounting for 9% to 55% of isolates. In addition, pneumococcal pneumonia is responsible for 11% to 37% of patients with CAP requiring admission to an intensive care unit and 6% to 26% of nursing home-acquired pneumonia. Risk factors for pneumococcal infections include immunosuppression (human immunodeficiency virus [HIV] infection, transplant recipients); immune deficiencies; aspiration (alcoholism, stroke, and seizure); sickle cell anemia; diabetic ketoacidosis; congestive heart failure; chronic obstructive lung disease; and crowding (jail, military, and nursing home).

Clinically, patients present with sudden onset of rigors, fever, pleuritic chest pain, and cough productive of rusty colored sputum. However, the presentation also can be more subtle and associated with predominantly nonspecific symptoms (e.g., malaise, coryza, and gastrointestinal symptoms). The diagnosis is confirmed by Gram's stain and culture of sputum; however, diagnosis can be difficult because the culture of pneumococci may simply reflect colonization of the upper airway. In addition, many patients have received antibiotics before sputum collection for culture and, therefore, may be culture negative. Other diagnostic tools such as blood cultures, bronchoscopically derived tracheal cultures, and serum pneumolysin antibodies may be useful. Radiographic patterns vary from lobar consolidation (usually unilobar, but occasionally two or more lobes are involved) to patchy diffuse opacities. Pleural effusions and empyema may be present; cavitation is rare. Overall mortality for hospitalized patients ranges from 7% to 36% and is influenced by age, comorbid illness, the presence of bacteremia, and the development of complications (e.g., respiratory failure, meningitis, empyema, or other organ failure).

Pneumococcal isolates with minimum inhibitory concentrations (MIC) below 0.1 μg/ml are classified as penicillin susceptible. Penicillin is the treatment of choice for patients with sensitive organisms. Amoxicillin is recommended by the Infectious Disease Society of America as appropriate outpatient oral treatment for pneumococcal pneumonia caused by penicillin-sensitive pneumococci. Alternative agents for penicillin-allergic patients include erythromycin, azithromycin, or one of the newer fluoroquinolones. Hospitalized patients should be treated with intravenous penicillin or ceftriaxone.

Pneumococci that are relatively resistant to penicillin have intermediate susceptibility to penicillin with an MIC of 0.1 to 1.0 μ/ml. Isolates that are highly resistant have MICs greater than 1.0 μ/ml. Penicillin-resistant *S. pneumoniae* were first reported in 1967 in New Guinea natives, followed in 1977 by a report of a multidrug-resistant strain. Currently, resistant strains are found throughout the world and they have developed resistance to several classes of antibiotic including trimethoprim-sulfasoxazole, tetracycline, erythromycin, choramphenicol, and quinolones. The recent increase in isolates that are resistant to penicillin is alarming. In 1997, the Centers for Disease Control (CDC) surveillance system for invasive pneumococcal disease revealed 11.4% of 2327 isolates were intermediate in susceptibility to penicillin and 13.6% were highly resistant to penicillin. Extremes of age (<18 months and the elderly), recent β-lactam use, overcrowding, malignancy, and human immunodeficiency virus positivity are risk factors for nonsusceptible strains. Since the development of relative resistance to penicillin involves lower affinity of penicillin binding proteins to β-lactams, cephalosporin sensitivity can also be affected. Nevertheless, cefotaxime and ceftriaxone are effective treatments for most pulmonary infections caused by pneumococci that are relatively resistant to penicillin, but strains resistant to these cephalosporins have been reported. A 10-year prospective study conducted in Barcelona of 504 patients with severe pneumococcal pneumonia revealed no significant difference in mortality rate between infections caused by penicillin-susceptible and relatively resistant strains when adjusted for other factors. The authors concluded that high-dose intravenous penicillin G may be effective for strains with intermediate susceptibility and that ceftriaxone or cefotaxime is effective for penicillin-resistant strains with MICs for cephalosporins that are less than 2.0 μ/ml.

For multidrug-resistant pneumococci with MICs greater than 2.0 μg/ml for cephalosporins, alternative agents such as vancomycin, clindamycin, imipenem, meropenem, or fluoroquinolones should be considered. For invasive disease, especially meningitis, recommendation is to add vancomycin to cefotaxime or ceftriaxone for initial therapy. Fluoroquinolones concentrate in respiratory tissue and may be useful in treating infections caused by pneumococci that are relatively resistant to penicillin, but their use is tempered by the recent evidence linking trovafloxacin to hepatoxicity and limited experience with grepafloxicin and moxifloxicin. Patients should begin to improve within 24 to 48 hours and recommended duration of therapy is 7 to 14 days.

Preventing pneumococcal infection is clearly an important goal in reducing morbidity and mortality. The 23 capsular antigen vaccine has been shown to be cost-effective and efficacious, although highly underutilized. It induces an antibody response within 1 week and remains active for 5 years in healthy adults. These 23 antigens represent 85% to 90% of the serotypes responsible for invasive pneumococcal infections based on surveillance data from the CDC. The CDC recommends vaccination for all persons aged 65 years or older, patients with functional or anatomic asplenia, and patients who are immunocompromised (e.g., HIV infection, hematologic malignancy, chronic renal failure or nephrotic syndrome, immunosuppressive therapy, or organ transplant recipient).

Other streptococci can also cause serious lung infections, albeit less commonly then pneumococcus. *Streptococcus pyogenes* (β-hemolytic, Lancefield group A) causes pyogenic infections such as pharyngitis, cellulitis, necrotizing fasciitis, arthritis, sepsis, toxic shocklike syndrome, and scarlet fever. *S. pyogenes* can result in severe necrotizing pneumonia and even empyema, especially in the postinfluenza or postmeasles setting and has been responsible for cluster outbreaks in military recruits and nursing home residents. *Streptococcus agalactia* (β-hemolytic, group B) is a common cause of neonatal infections such as sepsis, meningitis, and pneumonia. Group B, C, G, and *Streptococci viridans* are uncommon causes of pneumonia in adults.

Staphylococci are gram-positive bacteria that appear as clusters on Gram's stain. They are normal inhabitants of skin and mucous membranes, including the upper respiratory tract. The species that cause disease in humans are classified as coagulase-positive (*S. aureus*) or coagulase-negative (*S. epidermidis*, *S. saprophyticus*, and *S. hemolyticus*). *S. epidermidis* infection is almost always acquired in the hospital and coagulase-negative staphylococci are the major cause of catheter-related bacteremia. *S. epidermidis* can cause endocarditis, especially of prosthetic valves. *S. aureus* can cause severe pyogenic infections, including pneumonia, lung abscess, empyema, tracheitis, skin and soft tissue infections, endophthalmitis, osteomyelitis, septic arthritis, catheter-related bacteremia, and toxic-shock syndrome. *S. aureus* is isolated in approximately 3% of patients with community-acquired pneumonia, 15% to 20% of patients with nosocomial pneumonia, and up to 30% of those patients with nursing home-acquired pneumonia. Patients may initially describe symptoms of an upper respiratory tract illness. This is occasionally followed by a transient improvement with subsequent rapid progression to fevers, chills, cough, and chest pain. Risk factors for *S. aureus* pneumonia include diabetes, alcoholism, cystic fibrosis, bronchiectasis, and postinfluenza bacterial pneumonia. Presentation is characterized by high fever, productive cough with purulent sputum, and pleuritic chest pain. Radiologically, several patterns are seen (consolidation, diffuse or patchy infiltrates) and, classically, *S. aureus* pneumonia is known to cavitate. Diagnosis is made by culture and Gram's stain of sputum.

Staphylococci first developed resistance to penicillin in 1942 and later to the semisynthetic penicillins (e.g, methicillin) in 1961. Risk factors for acquiring methicillin-resistant *S. aureus* from the community include intravenous drug use, serious underlying illness, previous antibiotic therapy, and previous hospitalization. For strains sensitive to the semisynthetic penicillins, oxacillin, nafcillin, or first generation cephalosporins (e.g., cefazolin) should be used. Vancomycin should be used for penicillin-allergic patients (although it is less effective than penicillin derivatives) and for methicillin-resistant *S. aureus* infections. Therapy for staphylococcal pneumonia, especially for abscesses or other deep-seated infections, may require 4 to 6 weeks of antibiotics. Staphylococcal empyemas need to be drained via chest tube in addition to antibiotics for cure. Prevention remains a major emphasis for controlling staphylococcal infections. Strict handwashing

and careful attention to infectious control measures are of utmost importance in limiting the rate of nosocomial transmission.

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25. *HAEMOPHILUS INFLUENZAE* INFECTIONS

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Haemophilus influenzae are small, pleomorphic, nonmotile gram-negative rods, which occur in both encapsulated and nonencapsulated forms. The encapsulated forms (types a—f), and particularly *H. influenzae* type B (Hib), have increased virulence and are associated with invasive disease (e.g., meningitis, bacteremia, epiglottitis, pneumonia, and septic arthritis), primarily in children aged less than 5 years. In contrast, the genetically diverse unencapsulated (*nontypable*) strains of *H. influenzae* commonly cause community-acquired pneumonia, sinusitis, otitis media, and bronchitis. All strains of *H. influenzae* are fastidious, tend to be overgrown by other bacteria in culture, and require special growth factors (X, hemin and V, nicotinamide adenine dinucleotide) to grow aerobically. These factors can be supplied with chocolate or supplemented agars. The capsular forms are identified and differentiated from the nontypable *H. influenzae* strains by a variety of serotyping methodologies (e.g., latex particle slide agglutination, countercurrent immunoelectrophoresis). Although relatively accurate, these assays can misidentify a nontypable *H. influenzae* as encapsulated *H. influenzae*.

A dramatic shift has occurred in the epidemiology of *H. influenzae* infections in developed countries since the early 1990s, because of the universal implementation of Hib vaccines in infancy. *H. influenzae* type B was the cause of more than 90% of all invasive *H. influenzae* infections, with an estimated incidence of 1 of every 200 children; Hib-related disease is now uncommon in developed countries. Concurrently, there has been increasing global recognition of the importance of nontypable *H. influenzae* strains as causative agents for respiratory tract infections and, less commonly, for invasive disease.

Humans are the only known hosts for *H. influenzae*. The organisms, predominately the nontypable strains, colonize the nasopharynx throughout life, beginning in infancy. They can be cultured from 25% to 80% of asymptomatic individuals, depending on the population sampled. Higher rates and more prolonged duration of carriage are observed in those with underlying lung disease (e.g., cystic fibrosis, chronic obstructive pulmonary disease [COPD]) as well as in those with relative immunosuppression (e.g, alcoholism, diabetes). Colonization can be a very dynamic process, with co-infection and strain turnover within days to weeks. Unlike the nontypable strains, *H. influenzae* type B and other encapsulated strains colonize only a few percent of healthy individuals. The rate of carriage of Hib has substantially declined in countries using the Hib vaccine.

Bacterial transmission occurs via respiratory droplets or via contact with secretions and fomites. Increased transmission occurs in closed settings such as households and nursing homes. Pathogenesis of disease for the nontypable strains is by contiguous spread from a colonized nasopharynx, resulting in localized upper and lower respiratory tract infections. *H. influenzae*, primarily nontypable strains, cause approximately 20% of all otitis media infections in children and 20% to 25% of all sinus infections in adults. In addition, nontypable *H. influenzae* strains are second only to *Streptococcus pneumoniae* as the causative agents causing community-acquired pneumonia (12% to 28% of cases). Risk factors for *H. influenzae* pneumonia include (a) antecedent viral respiratory tract infection; (b) chronic lung disease (e.g., COPD or bronchiectasis); (c) systemic diseases associated with immunosuppression (e.g., diabetes or cancer); (d) environmental exposures (e.g., exposure to smoke); and in some cases, (e) strain-specific virulence factors. nontypable *H. influenzae* have several virulent strains, including a noncapsular phenotype with a virulence factor (Int-1) that appears transmissible.

The pathogenesis of disease is very different between encapsulated and unencapsulated strains. The encapsulated strains are better able to survive in the bloodstream, because the polysaccharide capsules, and in the case of *H. influenzae* type B, the polyribosylribitol phosphate moieties, confer virulence. Hib invades the nasopharyngeal vascular space; the ensuing bacteremia can result in sepsis, meningitis, epiglottis, and other deep-seated infections. Other encapsulated serotypes (especially a and f) can cause invasive disease, especially in the immunocompromised population and in a small minority of immunocompetent individuals. Unencapsulated strains of *H. influenzae* cause pneumonia, but only rarely cause tissue invasion. However, recent

reports from developing countries suggest that they are becoming more prevalent as causes of both invasive disease and pneumonia in healthy children and adults.

Nontypable *H. influenzae* commonly cause pneumonia in adults, which resembles other pneumonias in clinical presentation. Radiographically, often multilobar involvement occurs with patchy or lobar distribution of infiltrates. As with other bacterial pneumonias, bacteremia, parapneumonic effusions, and empyema can occur. Blood cultures and culture of other accessible specimens (e.g., parapneumonic pleural effusion) should be done, although the yield from blood cultures for nontypable strains is low. Gram's stain and culture of tracheobronchial secretions can be difficult to interpret, given the frequent colonization of the respiratory tract by *H. influenzae*. The diagnosis is supported if a predominance of gram-negative bacilli and polymorphonuclear leukocytes are seen in a Gram's stain of expectorated sputum (or transtracheal or bronchoscopic specimens). *H. influenzae*, however, may not be evident as the cause of pneumonia, by either Gram's stain or culture. More invasive sampling (e.g., protected bronchial brush catheterization or needle aspiration of lung tissue) can increase the likelihood of a definitive diagnosis. These procedures, however, are not usually necessary in stable, immunocompetent individuals presenting with community-acquired pneumonia. Rather, most patients are treated with empiric antibiotic therapy that covers the more common causes of community-acquired pneumonia.

Nontypable *H. influenzae* is also a common cause of exacerbations of COPD and bronchitis. The diagnosis is challenging, because the clinical signs can be subtle: low-grade fever; mild, increased shortness of breath; or a change in tracheobronchial secretions. Because of the ubiquity of the organism, as well as the limitations of sputum Gram's stain and culture (described above), empiric antibiotic therapy for COPD exacerbation should include coverage of nontypable *H. influenzae*.

Acute epiglottis, as with the other clinical syndromes primarily associated with *H. influenzae* type B, is declining in incidence; however, it is a presentation that requires prompt recognition and management to circumvent progression to lethal airway obstruction. Although acute epiglottitis is more common in children, it can also affect adults with serious clinical implications. It should be suspected in the setting of a severe sore throat and painful swallowing. In later stages, the voice is often muffled and stridor is evident with rapid progression to severe upper airway obstruction. The epiglottis is bright red and edematous when visualized by indirect laryngoscopy; it is seen as an enlarged structure compromising the air column on lateral roentgenograms of the neck. In expert hands, laryngoscopic evaluation can be performed with relative safety and is diagnostically helpful. Establishing a patent airway is essential until the edema and inflammation subside. Although tracheostomy will bypass the obstruction, management of the airway by endotracheal intubation is increasingly used such that tracheostomy is not usually required. However, manipulation of the swollen laryngeal tissues by attempts at visualization or intubation can result in more edema and obstruction; the provisions and expertise for tracheostomy should be immediately available. Management also includes appropriate antibiotics and may include systemic steroids, although the benefit of the latter has not been definitely established.

Serious infections with *H. influenzae* should be treated with parenteral antibiotics. Appropriate options include (a) some second-generation cephalosporins (i.e., cefuroxime); (b) third-generation cephalosporins (e.g., ceftriaxone, cefotaxime); (c) monolactams (i.e., aztreonam); (d) extended spectrum penicillins (i.e., piperacillin); and (e) imipenem-cilastatin. Less serious infections, including otitis media, sinusitis, bronchitis, and community-acquired pneumonia, can be treated with oral agents. A major consideration in selection of an oral agent is the occurrence of β-lactamase producing *H. influenzae* strains, which were first reported in the 1970s. Both encapsulated and nontypable strains can produce β-lactamase, and historically there has been a consistent increase in the prevalence of β-lactamase producing strains. The most recent national estimates suggest that approximately 35% of all isolates produce β-lactamase. Thus, ampicillin or amoxacillin are only appropriate when the particular isolate has been shown to be sensitive. Reasonable options for either empiric oral therapy or therapy with a documented β-lactamase producing strain include (a) trimethoprim-sulfamethoxazole; (b) cefuroxime axetil; (c) amoxicillin-clavulanate; (d) doxycycline; (e) azithromycin; and (f) fluoroquinolones. Erythromycin, first-generation cephalosporins, clindamycin, and

tetracycline all have poor activity against *H. influenzae* and should not be prescribed empirically.

Currently, a number of licensed *H. influenzae* type B conjugate vaccines incorporate capsular polysaccharide to protein carriers and are highly immunogenic, even in infancy. The Hib vaccines have been shown to be protective for invasive disease and to reduce carriage of *H. influenzae* type B, contributing to *herd immunity*. No cross-protection with other capsular strains or nontypable *H. influenzae* strains exists. Since the addition of these vaccines in the routine infant immunization schedule, follow-up surveillance has demonstrated marked reductions in the incidence of Hib infections (without concomitant increases in the prevalence of other encapsulated *H. influenzae* infections).

In summary, *H. influenzae* is an important respiratory tract pathogen with a changing epidemiology and resistance pattern noted over the last decade. Encapsulated forms, predominately *H. influenzae* type B, and nontypable strains are both pathogenic, however, with different mechanisms of disease pathogenesis and outcomes. The introduction of Hib immunization in infancy has sharply reduced the incidence of *H. influenzae* type B infections, which were predominately invasive infections of childhood. Nonencapsulated forms, which are common colonizers of the respiratory tract, cause primarily mucosal disease; they are responsible for a significant proportion of otitis media in children and sinusitis and community-acquired pneumonia in adults. Approximately 35% of both encapsulated and nontypable strains produce β-lactamase, so empiric antibiotic therapy should include agents resistant to β-lactamase. Research is in progress to develop an effective vaccine for nontypable *H. influenzae*.

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26. *KLEBSIELLA* PNEUMONIA

Bao Quoc Luu

Pneumonia caused by *Klebsiella* species (Friedlander's pneumonia) is classically, community acquired and found more often in middle-aged, alcoholic men. Presenting symptoms include the acute onset of prostration, pleuritic chest pain, dyspnea, high fever, and a productive cough sometimes yields *currant jelly* sputum. The physical examination generally suggests lobar consolidation (i.e., bronchial breath sounds, increased fremitus, and dullness on percussion). Findings consistent with pleural effusion and empyema also may be present. During the last decade, the classic presentation of *Klebsiella* pneumonia has evolved and now mostly manifests in the elderly, immunocompromised, and chronically ill as nosocomial pneumonia. Risk factors include the presence of diabetes mellitus, chronic obstructive pulmonary disease, and other immunosuppressive conditions such as hematologic malignancy, cytotoxic chemotherapy, steroid therapy, and neutropenia. Recent epidemiologic studies in the United States suggest that *Klebsiella* species is responsible for approximately 1% of community-acquired and 8% of nosocomial pneumonia.

Klebsiella species are ubiquitous nonmotile, gram-negative rods that commonly colonize mucosal surfaces of mammals such as human, horse, and swine. The organism contains a thick, gelatinous capsule that appears to increase its virulence. The most medically important species of the genus is *Klebsiella pneumoniae*; it causes most of the urinary, gastrointestinal, and respiratory tract infections. Some of the infection caused by this species is associated with *Klebsiella oxytoca*. The incidence of *Klebsiella* nasopharyngeal colonization ranges from 1% to 6% in the community; however, it increases dramatically in the hospital environment, where colonization rate is directly proportional to the length of stay. In the hospital setting, the principal reservoirs for transmission of *Klebsiella* organisms are the gastrointestinal tracts of patients and hands of hospital personnel. As with many other bacteria, strains of *Klebsiella* resistant to multiple antibiotics have emerged over the last two decades. Recently, *Klebsiella* strains have acquired plasmids from other members of the *Enterobacteriaceae* family that contain the extended-spectrum β-lactamase (ESBL) genes, imparting resistance to ceftazidime and other antibiotics. In the United States, the incidence of ceftazidime resistance is reported to be between 1.3% to 8.6%; the incidence is much higher in Europe.

Klebsiella organisms gain entry into the lower respiratory tract via aspiration of oral secretions. The most commonly affected areas of the lungs are the posterior segment of the right upper lobe and superior segment of the right lower lobe. In the initial phase of the infection, pathologic features of *Klebsiella* pneumonia are very similar to those of pneumoncoccal pneumonia. Homogeneous consolidation of an entire lobe is the most typical pattern. Patchy distribution, abscess formation, and cavitation are also seen. As infection progresses, *Klebsiella* organisms are more likely to cause parenchymal necrosis than *S. pneumoniae*. Large cavities containing fragments of necrotic lung

(pulmonary gangrene) may be found. Extension of parenchymal infection into the pleural space and empyema are more common in *Klebsiella* pneumonia than in pneumococcal pneumonia.

The classic radiographic finding in *Klebsiella* pneumonia, the *bulging fissure* sign, is observed in only 30% of patients with *Klebsiella* pneumonia; it has been observed in 10% of patients with pneumococcus pneumonia. In fact, because pneumococcal pneumonia is much more prevalent than *Klebsiella* pneumonia, on any given chest film the *bulging fissure* sign is more likely to be caused by pneumococcus than by *Klebsiella*. The *bulging fissure* sign has also been described in *Haemophilus influenzae* pneumonia, pulmonary tuberculosis, lung abscesses, and in *drowned lung* (consolidation associated with bronchial obstruction). Large series have shown that *Klebsiella* pneumonia is more likely to present as bilateral patchy parenchymal consolidation without cavitation or bulging fissures than as lobar consolidation of right upper lobe with a bulging fissure sign.

In general, patients presenting with community-acquired *Klebsiella* pneumonia are in acute respiratory distress and often require ventilatory support. Sputum Gram's stain reveals plump, gram-negative rods. Occasionally, the thick polysaccharide capsules can be visualized. Leukocytosis is common; however, a small percentage of patients may have leukopenia. Bacteremia occurs in approximately 25% of cases. In one recent retrospective review, all of the subgroup of 11 cases of alcoholics presenting with bacteremic *Klebsiella* pneumonia died. The mean duration of hospitalization to death was 24.6 hours, ranging from 5 hours to 4 days.

The presentation of hospital-acquired *Klebsiella* pneumonia may be less impressive. Depending on the patient's underlying illness and ability to respond immunologically, localizing symptoms, physical findings, and radiographic appearances may be less apparent or nonspecific. Occasionally, a patient may recover from the acute phase of *Klebsiella* pneumonia, but pass into a chronic phase of infection characterized by cavitation and scarring resembling that of tuberculosis. *Klebsiella* is frequently isolated from patients with lung abscesses, and, as with other lung abscesses, carries a relatively high mortality rate. One series reported the mortality rate of patients with *Klebsiella* lung abscesses as 44% compared with that of 50% and 83% in *Staphylococcus aureus* and *Pseumodmonas aeruginosa*, respectively.

The mortality rate for *Klebsiella* pneumonia remains high (25% to 50%) despite the advances in antibiotic treatment. Because of its fulminate course and its high mortality rate, prompt appropriate antibiotic therapy is essential. The correct microbiologic diagnosis can be used to guide therapy, so sputum and blood should be obtained early for culture and sensitivity. In cases of pleural effusion and possible empyema, pleural fluid should be sampled without delay. If *Klebsiella* pneumonia is suspected, empiric antibiotic therapy should be initiated, using a third-generation cephalosporin in combination with an aminoglycoside. In cases of suspected or documented strains with the ESBL, a carbapenem (e.g., imipenem or meropenem) is the antibiotic of choice. Combinations of β-lactam antibiotics and β-lactamase inhibitors (ticarcillin-clavulanic acid or piperacillin-tazobactam) can also be effective. These combinations have shown promising in vitro activities against ESBL-containing *Klebsiella*, but have not been entirely effective in animal models and some strains become resistant to the drug combination. Fluoroquinolone, aminoglycoside alone, and trimethoprim-sulfamethoxazole can be useful; however, many strains of ESBL-containing *Klebsiella* may also be multidrug resistant. The best method of preventing death from these resistant bacteria is to prevent nosocomial infection in the first place. Strict handwashing, isolation of patients with known resistant bacteria, as well as prudent use of extended spectrum cephalosporin are all important measures to prevent outbreaks of drug-resistant infections.

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27. OTHER GRAM-NEGATIVE PNEUMONIAS: PSEUDOMONAS AERUGINOSA, ESCHERICHIA COLI, PROTEUS, SERRATIA, ENTEROBACTER, ACINETOBACTER

James H. Williams, Jr.

The gram-negative bacilli (GNB), *Pseudomonas aeruginosa*, *Escherichia coli* and organism of the *Proteus*, *Serratia*, *Enterobacter*, and *Acinetobacter* species generally cause nosocomial, or hospital-acquired pneumonia (HAP). GNB are associated with less than 20% of pneumonias among ambulatory patients, most of which are caused by the more common *Klebsiella* species. However, GNB are the most common bacteria recovered

from the airways of debilitated, institutionalized patients with pneumonia and are responsible for about half of all deaths from bacterial pneumonia in this population.

Predisposing factors for GNB pneumonia vary with the population at risk. In the community, chronic bronchitis, bronchiectasis, alcoholism, diabetes, altered mental status, and neutropenia appear to be the major risk factors for GNB pneumonia. In the hospital, GNB pneumonia most commonly occurs following prolonged intubation, particularly in tracheostomized patients. Additional risk factors for nosocomial pneumonia include a prolonged hospital stay, usually in the intensive care unit (ICU); recent thoracic or abdominal surgery; advanced age; and severe underlying illness. Immunocompromised hosts are at particular risk for adverse outcomes from these infections.

The incidence of nosocomial GNB pneumonias appears to be rising, most likely because of increased airway colonization in susceptible inpatients. Although contaminated respiratory equipment has been held responsible for some outbreaks of pneumonia, particularly of *Serratia* and *Pseudomonas*, these outbreaks are uncommon with use of disposable equipment and aseptic techniques. In addition, some GNB pneumonias result from bacteremia following instrumentation with urinary and intravenous catheters, or from gastrointestinal or other remote sites; it is more common, however, for GNB to be delivered to the lungs via the upper airways.

The oropharyngeal or tracheal colonization by GNB that often precedes pneumonia is encouraged by a number of factors commonly encountered in the ICU. Among the most important are (a) alteration in body flora resulting from use of antibiotics to which these bacteria are resistant; (b) increased adherence of GNB to the airway epithelium of ill patients; (c) colonization of the upper airway and sinuses (including actual sinusitis); and (d) colonization of endotracheal tubes themselves. Some experts also contend that suppression of gastric acidity (for *stress ulcer* prophylaxis) promotes GNB proliferation in the stomach, leading to upper respiratory tract colonization. Regardless how GNB colonization occurs in individual patients, the institutional setting makes it particularly likely that the altered flora will be transmitted to other patients.

Access of nasopharyngeal flora to the lower airways is facilitated by a number of factors inherent to ICU patients. Translaryngeal intubation mechanically holds open the epiglottis and vocal cords; tracheal intubation, in general, decreases positive intrathoracic pressure during swallowing. While the endotracheal tube balloon cuff diminishes the rate at which aspirated secretions reach the lower airways, the reservoir of secretions continue to ooze around from above to below the cuff, which is kept at low pressure to avoid tracheal necrosis. Reflux around nasogastric tubes and a supine position may increase the volume of this reservoir. The normal reflex clearance of the airway is attenuated by central nervous system (CNS) depression (narcotics, sedatives, metabolic instability, CNS lesions); local reflex depression (topical anesthetic, learned tolerance of foreign nasotracheal or nasogastric tubes); or decreased effectiveness of the cough (postoperative pain, intubation, sedation). Mucociliary activity can be decreased (alcohol, chronic inflammation, metabolic disorders), and phagocytic activity can be impaired (immunocompromised patients, alcohol, overwhelmed reserves).

The clinical features of GNB infections are intertwined with the underlying diseases with which they are usually associated, which can affect signs and symptoms as well as radiographic appearance. The classic descriptions of GNB pneumonias focus on community-acquired cases. Although these descriptions incompletely represent the spectrum of nosocomial GNB pneumonias, they provide useful comparisons of these pathologic responses in otherwise relatively fit individuals. However, it is important to remember that immunocompromised patients, particularly those with granulocytopenia, may exhibit relatively few signs or symptoms; conversely, the appearance of pneumonia can be masked by similar signs and symptoms in patients with underlying acute lung injury.

Pseudomonas aeruginosa frequently colonize the skin or other mucosa of patients, and may be cultured in the hospital environment from soaps and liquid media, and on the mucosa of hospital staff themselves. It can colonize or infect tracheostomy sites, burns, wounds, and the urinary tract. Mucoid strains often emerge in the airways of patients with cystic fibrosis. Pneumonia, usually acquired via the airway, is predominantly located in dependent lung zones, whereas hematogenous infections may be more widespread. Pathologically, severe focal necrosis and hemorrhage progressing to

the formation of multiple small cavities is typical, with hemorrhagic or purulent pleural effusion often found at autopsy. Organisms can penetrate vascular walls and are associated with nodular infarcts. Clinically, patients usually appear toxic, presenting with chills, fever, and dyspnea. Pleuritic pain is uncommon, whereas sputum is often copious and can be blood-tinged. Patients with pseudomonas bacteremia occasionally develop ecthyma gangrenosum: a cutaneous maculopapular eruption that rapidly develops into hemorrhagic bullous, ulcerative, or nodular lesions. Initially thought to be pathognomonic for pseudomonas infection, it has been reported in bacteremia from other infections, including *Escherichia coli*, *Serrratia marcescens*, and a variety of bacteria and fungi. Radiographically, consolidation is usually present in one or more dependent areas, which can rapidly extend, coalesce, and develop abscesses varying in size from 2 to 11 cm. Hematogenous pneumonias are typically bilateral and present as diffuse patchy or nodular shadows. Small effusions may be present.

Escherichia coli pneumonia may follow aspiration or hematogenous dissemination from urinary tract or gastrointestinal infections. Pathologically, a diffuse, hemorrhagic pneumonia is often present, but abscess formation is uncommon. Clinically, patients generally appear toxic, with fever, dyspnea, productive cough, and often pleuritic chest pain. Some may show a relative bradycardia for the degree of temperature elevation and a paucity of signs of parenchymal consolidation. The chest roentgenogram usually demonstrates a patchy bronchopneumonia, often in lower lobes. Pleural effusion is common.

Proteus species uncommonly cause respiratory tract infection. Pulmonary infection is frequently associated with an altered state of consciousness, and probably acquired by aspiration. Pathologically, the pneumonia is hemorrhagic and associated with small abscesses. Clinically, the patients often appear less toxic, although chills, fever, dyspnea, productive cough, and pleuritic chest pain may be present. The chest roentgenogram demonstrates dense infiltrates, most often in the dependent segments of the upper lobes and superior segment of the lower lobes. Volume contraction may be seen. Pleural effusion is less common.

Pneumonia associated with *Serratia* species is also relatively uncommon. Clustered cases have been linked in the past to contaminated respiratory equipment. Pathologically, a diffuse bronchopneumonia can occur with small (2–3 mm) abscesses. Patients typically are toxic, with fever, chills, and productive cough. *Pseudohemoptysis*, the production of sputum tainted with a red pigment produced by some strains, is uncommon. The chest radiograph generally demonstrates a diffuse, patchy, bronchopneumonia similar to *Pseudomonas* pneumonia, although abscess formation is less common. Pleural effusion and empyema may occur.

Enterobacter pneumonia is less well characterized than the other GNB pneumonias. In one small series, symptoms included fever, dyspnea, and cough productive of yellow sputum, although pleuritic pain was uncommon. Chest radiographs most often demonstrate bilateral bronchopneumonia, but abscesses and empyema formation are uncommon. The emergence of drug-resistant strains has increased the frequency and seriousness of infection from these organisms.

Pneumonia associated with multidrug-resistant *Acinetobacter* species has recently emerged as a serious problem, probably because of the prolific use of broad-spectrum antibiotics. Colonization of hospitalized patients with these organisms is being observed with increasing frequency. The presence of multidrug-resistant *Acinetobacter* species in airway cultures of febrile intubated patients with pulmonary infiltrates presents diagnostic and therapeutic dilemmas. The chest roentgenogram may demonstrate multilobar infiltrates, occasionally with signs of necrosis (cavitation) or effusion.

The diagnosis of gram-negative pneumonia by examination of airway secretions is problematic, because of the frequency with which GNB colonize the airways of patients at risk, many of whom may have infiltrates on chest films for other reasons. Demonstrating numerous GNB on smears of airway secretions provides presumptive evidence (especially if multiple polymorphonuclear leukocytes are also present on the specimen), but does not reliably differentiate airway colonization from deeper infection. Quantitative bronchoalveolar lavage samples and the presence of intracellular organisms have been suggested to be more specific, but still may reflect bronchitis rather than pneumonia. Bypassing the oropharyngeal flora with protected bronchoscopic brushes and transtracheal aspirates can help to distinguish upper airway colonization from

peripheral alveolar infection, but lower airway colonization or contamination confound this distinction. These presumptive diagnoses are more firmly supported by a positive blood or pleural fluid culture. Occasionally, if the patient is deteriorating while undergoing treatment, demonstration of tissue infection from a lung biopsy specimen may be required for diagnosis.

Two issues that suggest different antibiotic strategies must be considered during the treatment of GNB pneumonia. First, the already high mortality is worsened by delayed use of antibiotics to which the organism is sensitive, arguing for the initial use of broad-spectrum coverage, particularly in patients sick enough to be admitted to the ICU. On the other hand, the emergence of antibiotic-resistant strains is promoted by use of antibiotics, arguing for limited use of antibiotics. One compromise is to start broad-spectrum antibiotics, based on the predicted resistance patterns in the local hospital, and then to narrow the coverage appropriately as culture results direct. Another approach is to rotate the classes of drugs selected routinely in a given hospital every few weeks or months to shift the emerging resistance patterns in the hospital, trying to protect classes of drugs with shared resistance patterns, while hoping to avoid multidrug resistance. Strategies must continue to evolve, with a concerted effort in each hospital.

Therapy with two synergistic antibiotics is commonly used for severely ill patients with GNB pneumonias (especially in patients with *Pseudomonas* species). The largest experience to date for treatment of *Pseudomonas* pneumonia has been with the combination of a broad-spectrum β-lactam antibiotic (e.g., a semisynthetic penicillin such as piperacillin or a third-generation cephalosporin such as ceftazadime) with an aminoglycoside such as gentamycin. However, aminoglycosides are associated with renal, otic, and neurologic toxicity. Adverse drug effects are more common in older individuals, in those with renal disease, and when aminoglycosides are used in combination with some other potentially toxic drugs (e.g., vancomycin). Combinations of semisynthetic penicillins and β-lactamase inhibitors (e.g., piperacillin-tazobactam) enhance efficacy against some organisms, but not *Pseudomonas*. Additional drugs include monobactams (e.g., aztreonam), thienamycin-derived carbapenems (e.g., imipenem or the less CNS toxic meropemem), and intravenous quinolones (e.g., ciprofloxacin), particularly when resistance or allergy to β-lactam drugs is an issue. The use of a single broad-spectrum drug (e.g., third-generation cephalosporin, thienamycin, or piperacillin-tazobactam) has been successful in the initial treatment of patients with fever and neutropenia pending results of cultures, unless concern for infection of a chronic central line supports additional coverage of skin organisms (*Staphylococcus* species).

A growing list of orally active agents effective against GNB has facilitated outpatient management of persons with less severe pneumonia. Options include quinolones with *Pseudomonas* activity (e.g., ciprofloxacin) and less broad second- and third-generation cephalosporins, as well as β-lactam inhibitor combinations (e.g., amoxicillin plus clavulanate). Therapy should be tailored to the individual situation, with special attention paid to the patterns of antibiotic sensitivity and the possibility of drug resistance.

Airway instillation of aminoglycosides as an adjuvant to intravenous therapy more rapidly clears GNB from secretions, but the impact this therapy has on the on the overall course of intubated patients with pneumonia is far from certain. In contrast, repeated nebulization of very high doses of tobramycin has improved outcomes among outpatients with cystic fibrosis, and this approach is under investigation for patients with other types of bronchiectasis.

The potential role of passive immunotherapy in both the treatment and prevention of GNB infections continues to be investigated. However, variable and often disappointing results have emerged from clinical trials and the data from any one study should be interpreted with caution. Strategies such as the treatment of sepsis syndrome with antibodies against endotoxin and tumor necrosis factor, or enhancement of host responses with granulocyte colony-stimulating factor in infected (but immunologically normal) patients have not improved survival. However, marrow stimulation with granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor remain important adjuvant therapies for neutropenic patients with infections.

Further development of therapeutic options may decrease the high mortality rate associated with GNB pneumonia, which ranges from 20% to 90% and appears related mainly to the severity of the underlying illness. Bacteremia itself is not necessarily

associated with higher mortality in most patients. However, in neutropenic patients, bacteremia from *P. aeruginosa* pneumonia carries a mortality rate exceeding 80%. Supportive measures directed at the underlying illnesses and concurrent multiorgan dysfunction are likely important for overall outcome.

A persistently high mortality rate from GNB pneumonia continues to stimulate interest in preventative therapy. Careful cleansing of hands and other contacted surfaces (e.g., stethoscopes) are too often forgotten when moving from patient to patient. Although clearance of condensate in ventilator tubing is recommended, frequent replacement of the tubing itself has little impact. Prophylactic administration of antibiotics intratracheally, intravenously, or by oral paste to achieve *selective gut decontamination* can reduce colonization with susceptible organisms, but resistant strains appear and mortality has not been consistently improved. Among high-risk patients, elevation of the head of the bed appears important, whereas the role of gastric alkalinization for stress ulcers is still debated. Avoidance of prolonged nasotracheal intubation and early recognition and treatment of sinusitis may diminish associated pneumonia. Avoidance of intubation with noninvasive (mask) ventilation may reduce the incidence of HAP, but the benefit of this approach is still controversial. The potential value of augmenting immune responses in high-risk patients continues to be explored, including active immunization of high-risk individuals, and passive enhancement of host responses in established infections. Dietary supplements to restore micronutrient deficiencies (e.g., selenium, zinc) may enhance host immunity and reduce the risk of infection. Continued basic and clinical research in this area hold the promise of reducing the as yet unacceptably high mortality rate caused by infection with GNB.

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28. ANAEROBIC PULMONARY INFECTIONS

Jayne E. Chu

Anaerobic infection is relatively common in the lung and pleural space. Anaerobic bacteria, which have been isolated in 85% to 93% of lung abscesses and in 29% to 76% of empyemas, are a major cause of both community-acquired and hospital-acquired pneumonias. However, the role of anaerobic pathogens in pulmonary infections is often overlooked because of the difficulty in isolating and culturing these organisms.

Blood cultures are positive in less than 3% of anaerobic pulmonary infections. Adequate specimens for culture are difficult to obtain because of the ubiquity of anaerobic bacteria in normal oropharyngeal flora. Expectorated sputum and bronchoscopy aspirates are often contaminated by oropharyngeal flora. Transtracheal aspirates, transthoracic aspirates, and quantitative protected brush specimens, all of which avoid contamination from the upper airway, are difficult to obtain under the anaerobic conditions necessary for culture. (An empyema sample, however, can be collected by thoracentesis anaerobically.) Because of the limitations of culture techniques, most anaerobic infections are diagnosed presumptively, based on the clinical presentation.

Anaerobic pulmonary infection is caused by aspiration of oral secretions, direct extension from continuous foci such as subphrenic abscesses, or via the bloodstream. More than 70% of cases are caused by aspiration. Aspiration is commonly associated with states of impaired consciousness such as alcoholism, cerebrovascular disease, drug overdose, general anesthesia, head trauma, or seizure disorder. Other predisposing conditions include neuromuscular disease, esophageal dysmotility, intestinal obstruction, use of nasogastric or orogastric tubes, periodontal disease, gingivitis, and smoking (which compromises the activity of respiratory cilia). The most common sites of infection are the dependent portions of the lung: if aspiration occurs in the recumbent position, the posterior segments of the upper lobes and superior segments of the lower lobes are generally involved; if aspiration occurs in the upright position, the basal segments of the lower lobes are involved. When infection develops in other pulmonary segments, an underlying process other than aspiration (e.g., bronchial obstruction or metastatic infection) should be suspected.

The most common bacteria causing anaerobic infections resemble *mouth flora* found in the gingival crevice, with *Fusobacterium nucleatum*, *Peptostreptococcus* species, and *Prevotella melaninogenicus* the predominant organisms. *Bacteroides fragilis* is a notable exception. It is isolated in 7% to 21% of anaerobic infections and is not commonly present in the oropharyngeal cavity. Unlike aerobic pneumonias, most anaerobic infections are polymicrobial, with an average of three organisms per infection. In approximately half of anaerobic infections, only anaerobic bacteria are recovered. The remaining half have aerobic bacteria concurrently present, although no specific clinical characteristics distinguish between infections involving exclusively anaerobic bacteria and those with anaerobic–aerobic mixtures. Aerobic bacteria associated with anaerobic infections include *Klebsiella* species, *Staphylococcus aureus*, *Streptococcus* species, and *Haemophilus influenzae*. Hospital-acquired aspiration pneumonia is more likely caused by mixed aerobic–anaerobic infections in which the aerobic component is often gram-negative rods.

Because the bacteriology of most anaerobic pneumonias is similar, the degree of virulence depends on the host factors and the size of inoculum. Although aspirating small amounts of mouth contents is relatively common, infection usually does not occur because anaerobic bacteria found in the oropharynx are generally less virulent. However, aspiration can lead to pneumonia if either (a) large amounts of oropharyngeal secretions are aspirated or (b) chronic infections in the gingivodental crevice increase the concentration of anaerobic bacteria in the mouth. Anaerobic pneumonias can also occur when focal areas of the lung are subject to tissue necrosis or stasis of secretions from conditions such as pulmonary infarction, bronchial obstruction (due to a foreign body or neoplasm), or bronchiectasis. Underlying conditions that compromise host defense (e.g., malnutrition, diabetes mellitus, steroids, and cytotoxic agents) are also risk factors for anaerobic lung infection.

The clinical course of anaerobic pulmonary infections is progressive, and the natural history of uncontrolled disease can be divided into several distinct stages: (a) pneumonitis, (b) necrotizing pneumonia, (c) abscess formation, and (d) empyema. Pneumonitis mimics common bacterial aerobic pneumonia with an acute presentation of fever, cough, pleuritic chest pain, and patchy infiltrates seen on chest x-ray film. The only distinguishing features of acute anaerobic infection are putrid sputum, which is found rarely, the absence of rigors, and an underlying predisposing condition in most patients. If the anaerobic infection is treated promptly at this point, the pneumonitis resolves and there are no residual lesions. Necrotizing pneumonia can develop after 7 to 16 days if the anaerobic pneumonitis is untreated or unchecked by normal host defenses. This is a more subacute presentation, with patients usually having symptoms

for more than a week before presentation. Signs and symptoms include fever, pleuritic chest pain, putrid sputum, and multiple microabscesses (<1 cm in diameter as seen on chest x-ray film). The response to treatment at this stage of infection is slow, and pulmonary complications are frequent. Large lung abscesses can form if the microabscesses enlarge and coalesce. This is an indolent stage of the infection, which can mimic tuberculous infection or lung cancer. Patients usually present after several weeks of symptoms, with fever, anorexia, weight loss, anemia, pleuritic chest pain, putrid sputum, clubbing, and thick-walled cavitary lesions (>1 cm as seen on chest x-ray film). If infection still remains uncontrolled, the next stage is empyema, which develops as the necrosis extends to the pleura. A bronchopleural fistula can occur if the necrosis communicates with the airways.

Treatment of anaerobic pulmonary infections is usually empiric because it is difficult to obtain specimens that are valid and meaningful for anaerobic culture. Special techniques are required for transport and processing of specimens, and extended periods of time are required to isolate anaerobic organisms in culture. Even when appropriate specimens are collected and rigorous culturing techniques are used, most laboratories do not perform in vitro sensitivity testing on anaerobes. Most importantly, most infections involve three to five microbial species and the pathogenic potential of each one may be uncertain. The National Committee for Clinical Laboratory Standards does not recommend routine sensitivity testing of anaerobic bacteria; empiric treatment of anaerobic pulmonary infections is usually effective without it.

The three most commonly recommended antibiotic regimens for anaerobic pulmonary infections are penicillin, clindamycin, and the combination of metronidazole plus penicillin. In the 1960s, nearly all anaerobic pulmonary infections were treated with penicillin and there were very few treatment failures. Although penicillin has proved to be an effective treatment for anaerobic pulmonary infections, in vitro sensitivity testing demonstrates that 15% to 25% of patients have strains that are resistant to penicillin because of the production of β-lactamases, most commonly *Prevotella*, as well as *Fusobacteria*. Clindamycin, however, is effective against the β-lactamase–producing pathogens. One large prospective study comparing antibiotic regimens for the treatment of anaerobic lung abscesses found a statistically significant difference favoring clindamycin over penicillin in terms of number of treatment failures, number of relapses, mean duration of fever, and mean duration of putrid sputum. However, treatment with penicillin is still the drug of choice for some clinicians because of its low cost, and because clinical failures with penicillin are rare. Another antibiotic for the treatment of anaerobic infections is metronidazole, which has bactericidal activity against virtually all anaerobes and good penetration into abscess cavities (and through the blood–brain barrier). However, treatment of anaerobic lung infections with metronidazole alone has been associated with an unacceptably high proportion of treatment failures, possibly because of its poor activity against co-existing aerobic and microaerophilic streptococci. Thus, metronidazole is a viable treatment option for anaerobic infections only when used in combination with penicillin.

The treatment duration necessary for an anaerobic lung infection must be individualized, because the rate of response to therapy can vary. Patients with uncomplicated pneumonitis usually show signs of resolution within the first few days of treatment, whereas those with necrotizing pneumonia and abscesses may take weeks to improve. Response to treatment of patients with empyema may be extensively delayed and fevers can recur and persist if the empyema is not completely drained. Parenteral antibiotics are usually given initially; oral medications can be substituted once the fever and signs of toxicity have subsided. Oral (outpatient) therapy usually continues for at least 6 to 12 weeks. Chest radiographs are obtained at intervals of 2 to 4 weeks. Treatment should continue until radiographic healing has occurred: when radiographs demonstrate complete resolution of parenchymal opacities or show only stable, residual scars.

Antibiotics are the main element of treatment for anaerobic lung infections. Although empyema almost always requires surgical drainage, lung abscesses usually resolve with antibiotics alone; drainage can even be hazardous because of risk of bacteria spillage into other pulmonary segments. Fiberoptic bronchoscopy is indicated to rule out bronchial occlusion as a cause of lung abscess when occlusion is suspected, either on clinical grounds or because the abscess fails to resolve within a reasonable time. Surgical intervention may be required in up to 10% to 12% of lung abscesses, and

is indicated under the following circumstances: (a) rapid enlargement of the abscess despite antibiotics; (b) life-threatening hemorrhage caused by erosion into a major blood vessel; (c) bronchial obstruction with poor drainage; (d) symptomatic bronchiectasis; or (e) associated lung cancer. Some patients with urgent needs for abscess drainage may, however, have prohibitive operative risks. A suggested approach in such cases is percutaneous drainage of pulmonary abscesses, which has been successful in some severely septic and debilitated patients.

The mortality rate for untreated anaerobic pulmonary infections is 30% to 35%; it is reduced to 5% to 10% with antibiotics and other appropriate therapy. Inadequate or delayed effective therapy may allow the progressive destruction of parenchymal tissue, resulting in bronchiectasis, pulmonary fibrosis, chronic empyema, persistent bronchopleural or pleurocutaneous fistula, and recurrent pulmonary infection. In addition, the infection can disseminate to distant sites, particularly to the brain. Conditions associated with poor prognosis include large abscess cavity size, necrotizing pneumonia, prolonged symptoms lasting more than 8 weeks, advanced age, bronchial obstruction, and comorbid diseases. However, with prompt diagnosis and effective treatment, the prognosis for anaerobic pulmonary infections has generally been favorable.

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29. EMPYEMA

Carl A. Riddick

Empyema can be defined as the presence of pus or infected fluid in the pleural space. It remains a frequent source of morbidity and mortality, although it is less common since the advent of effective antimicrobial chemotherapy. Pulmonary parenchymal infection is the most common cause of empyema; postsurgical, posttraumatic, and iatrogenic causes are encountered with increasing frequency. Less common causes include bacteremic seeding of the pleural space, septic emboli from distant sites of infection, esophageal perforation, and direct extension from perithoracic sites of infection (e.g., subphrenic abscess). Of cases, 30% to 35% are estimated to be nosocomial in origin. *Streptococcus pneumoniae* remains the most commonly isolated organisms, but *Staphylococcus aureus*, gram-negative enteric organisms, and anaerobes are now increasingly isolated. Many cases are polymicrobial. Anaerobic organisms are responsible for 11% to 76% of reported cases, depending on the series and the fastidiousness of the search for anaerobes. The incidence of opportunistic and unusual organisms has also increased, coincident with the increasing numbers of patients seen with underlying immunodeficiency.

Pathologically, untreated parapneumonic empyema progresses through three phases of variable duration. The initial response to an underlying parenchymal focus of infec-

tion is the exudation of sterile fluid across the visceral pleura into the pleural space. This fluid is thin, free flowing, and characterized by a low white blood cell count and normal pH and glucose concentration. This so-called *exudative phase* can last from hours to days. During the next (fibrinopurulent) phase, polymorphonuclear leukocytes accumulate in the fluid in response to the invasion and multiplication of microorganisms. During this phase, pleural fluid increases in volume, and pH and glucose concentration fall, which is associated with a rise in lactic dehydrogenase (LDH) caused by cellular metabolism and lysis. The pleural fluid subsequently thickens, fibrin is deposited on both pleural surfaces, and a tendency is seen toward loculation and the formation of a limiting membrane (i.e., the pleural peel). After a variable interval ranging from days to weeks, the organization stage begins, characterized by the migration into, and increased activity of, fibroblasts in the developing membrane, which leads to the formation of the inelastic pleural peel. Untreated, empyema rarely resolves and it can spontaneously rupture into lung parenchyma (bronchopleural fistula) or through the chest wall (empyema necessitatis). The inflammatory response is largely orchestrated by the release of soluble mediators of inflammation from both resident and recruited inflammatory cells, including the mesothelial cells lining the pleural surfaces.

Empyema should be considered whenever pneumonia is suspected and a pleural effusion is detected. The clinical presentation is nonspecific and frequently conditioned by host factors, including associated disease processes, the immune status of the host, and coincidental medical therapy. Fever, cough, dyspnea, pleuritic chest pain, and leukocytosis are common but not always present. Empyema can also present as an indolent process with malaise, low-grade fever, weight loss, and anorexia. Patients with postpneumonectomy empyema can develop postoperative fever, expectorate large quantities of purulent sputum, and develop purulent drainage from the thoracotomy wound. A mediastinal shift can occur. Debilitated patients and patients on corticosteroid and other immunosuppressive therapy can be afebrile and the peripheral blood leukocyte count may not be elevated.

The chest radiographs of patients with pneumonia should be carefully inspected for the presence of pleural fluid. If a pleural effusion is noted or suspected, decubitus views should be obtained to confirm its presence, to estimate the volume of fluid, assess for loculation, and further assess the underlying parenchyma. Radiographic findings are not specific for the different causative organism(s), but can have prognostic value. Fluid that is not free flowing on decubitus views or is present in fixed or nondependent locations suggests loculation. An air–fluid level is associated with empyema caused by a gas-forming organism, bronchopleural fistula, or lung abscess abutting the pleural space.

Ultrasound can be used as a substitute for, or as an adjunct to, decubitus radiographs. Ultrasound has several applications, including the evaluation of complicated collections for loculations, localization of fluid for thoracentesis, and guidance for the placement of thoracostomy tubes. Contrast-enhanced chest computed tomography (CT) scanning is superior to plain chest radiography and ultrasonography in defining the empyema space and assessing adequacy of drainage. CT assessment of pleural thickening and the attenuation of subpleural fat have been shown to be both sensitive and specific for empyema in patients with parapneumonic effusions. CT is also useful for differentiating lung abscess from empyema with bronchopleural fistula. Despite their obvious utility, the optimal roles of CT and ultrasound in the initial evaluation remain unclear.

Diagnostic thoracentesis is nearly always required for patients with pneumonia and large pleural effusions, because clinical parameters alone do not allow the clinician to reliably differentiate effusions requiring drainage (so-called *complicated parapneumonic effusions* and empyema) from those likely to resolve with antibiotic therapy alone (uncomplicated effusions). However, if the pleural fluid layers to less than 1 cm on decubitus view, further diagnostic intervention is usually not necessary. When thoracentesis is performed, the fluid should be carefully collected and visually inspected. The gross appearance of the aspirated fluid in pleural space infections ranges from thin and nonpurulent to thick and putrid. The latter is associated with anaerobic infection and is virtually diagnostic. The fluid should be sent to determine pH, differential leukocyte count, and the appropriate stains and cultures. If the pH is not available, glucose and LDH concentrations should be measured. In the setting of a free-flowing parapneumonic effusion, a carefully obtained pH (collected anaerobically in a heparinized

syringe and quickly placed on ice), glucose, and LDH are commonly used to determine therapy. A pleural fluid pH greater than 7.3 is usually associated with a positive response to antibiotic therapy alone, whereas a fluid pH less than 7.2, glucose less than 30, LDH greater than 1500, and the presence of loculation suggest the need for early surgical (chest tube) drainage. Patients having free-flowing effusions with a pH between 7.2 and 7.3 can be started on antibiotic therapy alone and monitored. A repeat thoracentesis in 12 to 24 hours and clinical parameters can then be used to further guide therapy. Increasing pleural fluid, continued signs and symptoms suggestive of pleural sepsis, and falling pH and glucose suggest the need for drainage.

The use of biochemical parameters should augment, not replace, clinical judgment regarding the optimal treatment of parapneumonic effusions. The threshold for consideration of tube drainage needs to be individualized according to the patient's estimated risk for complicated effusion, empyema, and the likelihood of poor outcome. Pleural fluid Gram's stains and cultures are occasionally negative, especially in the setting of prior antibiotic therapy. In addition, pleural fluid in loculated effusions may not be homogeneous: fluid sampled from one locule can have unremarkable biochemical parameters and stain negative, whereas fluid in other locules can have features that suggest the need for drainage. Multiple diagnostic thoracenteses occasionally are necessary for loculated effusions. Finally, pleural fluid biochemical parameters do not carry the same prognostic significance in the setting of other processes known to produce effusions with a low pH, in particular, rheumatoid pleuritis, tuberculous pleurisy, and malignancy.

Antibiotic therapy and complete pleural space drainage are the mainstays of initial therapy for pleural empyema. The initial choice of antibiotics should be based on the clinical presentation, underlying pathologic processes, and the results of microbiologic stains. Anaerobes are commonly present in empyemas and empiric antibiotic regimens should include therapy directed against them. Keeping these facts in mind, several drug regimens may be effective, including (a) modified penicillin/β-lactamase inhibitors combinations; (b) clindamycin plus a third-generation cephalosporin (or aztreonam); and (c) penicillin, metronidazole, and ceftazidime. For nosocomial or other suspected gram-negative empyemas, a fluoroquinolone such as ciprofloxacin, a third-generation cephalosporin or a broad-spectrum penicillin/β-lactamase inhibitor combination should be considered. Imipenem or meropenem can also be used as *monotherapy*. Although most antibiotics adequately penetrate into the infected pleural space, aminoglycosides penetrate less well and can be inactivated in the milieu of an empyema; they are not appropriate monotherapy. As with any infection, antibiotic therapy should be conditioned on the local susceptibilities of the commonly encountered organisms and adjusted once culture and sensitivity results are available. Therapy duration depends on the clinical circumstances; however, as in other necrotizing intrathoracic infections, antibiotics should be continued until clinical and radiographic evidence is seen of resolution of infection.

Prompt and adequate drainage is indicated for effusions with (a) a positive pleural fluid Gram's stain or culture; (b) those with frank pus on thoracentesis; (c) those with loculations noted on imaging studies; and, (d) in the case of parapneumonia effusions, those with a pleural fluid pH less than 7.2. (A possible exception is empyema associated with pneumococcal infection, for which some experts recommend antibiotic therapy alone.) For free-flowing or uniloculate effusions, closed thoracostomy tube drainage is usually adequate. A large bore (28 to 36 Fr) chest tube should be placed in the dependent portion of the pleural space by one experienced in this procedure. After placement, adequacy of drainage should be confirmed by appropriate imaging studies, usually posteroanterior and lateral chest radiography. Fibrinolytic therapy, with urokinase or streptokinase, has been used with success and a trial of this therapy may be considered after initial failure by chest tube drainage, especially for loculated effusions. Urokinase may avoid the risk of allergic reactions observed with streptokinase.

For more complex effusions and for empyemas unresolved after chest tube placement, a variety of surgical drainage techniques are available for more definitive management. Thoracoscopy has become a popular initial approach for patients with nonresolving effusions. It has the advantage of allowing direct visualization of the pleural space, lysis of adhesions, and optimal placement of chest tubes. If a pleural peel is present at thoracoscopy, the decision can be made to proceed directly to a standard thoracotomy and pleural decortication. *Minithoracotomy* with digital lysis of adhesions and thoracostomy

tube placement is another commonly used technique. For the most complex pleural space infections or after the development of a pleural peel, recommendation is to proceed directly to a standard thoracotomy and decortication. This approach may shorten hospitalization and the duration of chest tube drainage and can usually be performed with reasonable safety, even when the duration of empyema is unknown. For patients too debilitated to undergo decortication, open drainage, with or without an Eloesser flap, can be an effective alternative, albeit one that is frequently associated with prolonged hospitalization. Surgical repair using a muscle or omental flap may be necessary for a bronchopleural fistula-associated empyema unresponsive to aggressive tube drainage, or for an empyema complicating a pulmonary resection. Thoracoplasty can also be considered in these settings.

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30. ATYPICAL PNEUMONIAS: MYCOPLASMA, CHLAMYDIA, Q FEVER, AND *LEGIONELLA*

Philip A. LoBue

Historically, the appellation, *primary atypical pneumonia* was applied to pulmonary infection that differed clinically and radiographically from the *classic* bacterial lobar pneumonia. Subsequently, a variety of organisms were found to be responsible, including *Mycoplasma pneumoniae*, *Chlamydia psittaci* (causing ornithosis or psittacosis), *Chlamydia pneumoniae* (formerly *C. psittaci*, strain TWAR), *Coxiella burnetii* (causing Q fever), *Legionella*, and various viruses. These *atypical* agents cause pneumonia quite commonly—more commonly, taken as a whole, than pneumococcus, and they account for less than half of all community-acquired pneumonias. Although they differ in their epidemiology and natural history, they are transmitted via particle or droplet inhalation in contrast to pneumococcal disease, which is usually carried into the oropharynx and then aspirated into the lungs.

Mycoplasma pneumoniae accounts for 10% to 35% of pneumonias in ambulatory patients. Mycoplasma are members of the class *Mollicutes* and are the smallest free-living organisms. *M. pneumoniae* appears to be endemic to humans, with an incuba-

tion period averaging 14 to 21 days. Although perceived to be a disease of healthy young adults, one study of hospitalized patients with community-acquired pneumonia in Ohio found that the incidence of *Mycoplasma* infection increased with age, demonstrating that it is also an important pathogen in the elderly. The infection is usually endemic, but epidemics do occur, especially in the winter months, and appear to have a periodicity of 3 to 5 years. The rate of infection is greatest in areas of close personal contact (e.g., military bases, fraternity houses) and within families. Infection rates are usually high in such groups, but only a few patients develop clinical pneumonia. Studies in military recruits reveal an extraordinarily high incidence of infection (up to 75%), as judged by seroconversion during 3 to 4 months of basic training; however, only 3% to 6% with seroconversion develop symptomatic pneumonia. A carrier state can be present for up to 4 months.

In addition to pneumonia, *M. pneumoniae* can cause bronchitis, myringitis, and a pharyngitis that is clinically indistinguishable from streptococcal pharyngitis. Along with certain viral infections, the organism also is associated with an increased incidence of asthma attacks in older children. Extrapulmonary manifestations uncommonly occur. The best known is cold agglutinin-induced hemolysis, which results from immunoglobulin M (IgM) antibodies that cross-react with the I antigen of red blood cells. Raynaud's syndrome, peripheral gangrene, and disseminated intravascular coagulation (DIC) have developed in this setting. Uncommon complications include hepatitis, erythema multiforme, the syndrome of inappropriate antidiuretic hormone, pericarditis, myocarditis, and neurologic abnormalities, including aseptic meningitis, meningoencephalitis, transverse myelitis, and, possibly, Guillain-Barré syndrome. The overall mortality rate is 0.1%, which is largely accounted for by neurologic and cardiac involvement. Overall, only 2% of patients with *M. pneumoniae* require hospitalization.

The bacterial genus *Chlamydia* contains three species: *C. trachomatis*, *C. psittaci*, and *C. pneumoniae*. These are small gram-negative obligate intracellular organisms that, unlike viruses, synthesize both ribonucleic acid and deoxyribonucleic acid and reproduce by binary fission. *C. trachomatis* causes conjunctivitis and pneumonia in newborn infants but is not a cause of adult respiratory disease.

Chlamydia psittaci is primarily an avian pathogen that causes infection in humans (ornithosis or psittacosis) after contaminated droppings from diseased birds are inhaled. Despite this, many series document that only a few infected patients recall any avian exposure. The term *ornithosis* is preferable to psittacosis because the organism can be transmitted by a number of birds other than by the psittacine (parrot) family. Parrots and parakeets are the most common sources of human infection, but domestic (chickens, ducks, and turkeys) and urban (pigeons) fowl can also transmit infection. Ornithosis occurs sporadically but frequently is seen associated with avian outbreaks. It is a serious occupational hazard in poultry-processing plants, with turkeys being the most commonly involved bird in the United States and ducks, in Europe. After the organism gains access to the upper respiratory tract, it spreads hematogenously to the lungs and to the reticuloendothelial system. The incubation period is 7 to 14 days. Human-to-human transmission occurs but is unusual. Respiratory isolation, however, should be practiced for hospitalized patients because healthcare workers have contracted the disease.

The clinical spectrum of ornithosis, which is quite variable, includes (a) a flulike illness (the majority); (b) pneumonia that, although generally mild, can be a severe multilobar consolidative process characterized by splenomegaly and relative bradycardia; and (c) a fulminant toxic syndrome resembling typhoid. Common extrapulmonary manifestations include severe headache, photophobia, myalgias, arthralgias, nausea and vomiting, hepatosplenomegaly, and epistaxis. Less commonly, endocarditis, myocarditis, disseminated intravascular coagulation, and thyroiditis are seen. High spiking fevers, shaking chills, severe headache, and stupor characterize severe ornithosis. A macular rash (*roselike* or Horder's spots), lymphadenopathy, and hepatosplenomegaly occasionally occur. Poor prognostic signs include increased age, confusion, leukopenia, severe hypoxia, and renal and multiple lobar involvement. Renal failure and jaundice signify fulminant infection. The mortality rate was 20% before the antibiotic era and is now 5% with treatment.

Chlamydia pneumoniae is increasingly recognized as a significant cause of respiratory illness. Initially thought to be a strain of *C. psittaci*, it has now been demonstrated by antigenic analysis, DNA studies, and ultrastructural views of the *elementary body*—

its extracellular infecting form—to be a separate species. In contrast to *C. psittaci*, an animal vector (other than humans) has not been documented. Mounting serologic evidence indicates that infection is common throughout the world. It has been seen in military populations and is endemic. Studies in a college population indicated that 12% of pneumonias and 5% of the episodes of acute bronchitis could be attributed to this organism. The illness is clinically similar to *Mycoplasma* species infection. Fever and cough are common, with pharyngitis in up to 50% of patients. Other clinical syndromes include sinusitis and tonsillitis. Pleuritic chest pain is unusual. The patient has a brief prodrome of headache and myalgias and then high fever and shaking chills. Cough, pleuritic chest pain, watery diarrhea, and delirium are frequently seen.

Coxiella burnetii, the causal agent in Q fever, is an obligate intracellular parasite with a large natural reservoir that includes rodents, cattle, sheep, and goats. In nature, a tick vector maintains the disease. Humans acquire the disease through contact with infected milk, feces, urine, or placentas of farm animals. The disease is virtually nonexistent in urban areas but can be spread in a rural community by contaminated dust, hay, and clothing. Human-to-human spread, although theoretically possible, has never been documented. The incubation period averages 2 to 3 weeks. Epidemics have been reported in stockyard and meat packinghouse employees, dairy workers, animal hair processors, and medical school employees (in research facilities using contaminated sheep placentas). Many cases of Q fever appear to be flulike with high fever, cough, headache, and myalgias. Significant pulmonary symptoms occur in up to 50%. Other more severe extrapulmonary disorders include endocarditis with a predilection for the aortic valve, myocarditis, and pericarditis. Endocarditis can occur in up to 11% of infected patients and can appear months or years after the initial infection. Q fever pneumonia is usually a self-limited illness with a mortality rate of less than 1%.

Legionnaires' disease is an acute pneumonic illness caused by gram-negative bacterial organisms of the genus *Legionella*. At present, approximately 40 species of *Legionella* are known. Most cases of Legionnaires' disease have been caused by *Legionella pneumophila*, serogroups 1 to 4, but other species known to cause similar human disease include *L. bozemanii*, *L. micdadei* (Pittsburgh pneumonia agent), *L. dumoffii*, *L. longbeachae*, *L. jordanis*, *L. oakridgensis*, *L. feeleii*, *L. maceachernii*, and *L. hackeliae*. *Legionella* organisms are mainly intracellular parasites, distinguished by their very weak gram-negative staining and fastidious growth requirements in culture. The organisms are found in water sources such as cooling towers, evaporative condensers, humidifiers, and nebulizers. Superheating (≥50°C) and hyperchlorination eradicate the organism. *Legionella* can be an opportunistic pathogen. Patients with immunosuppression are at increased risk for infection, although outbreaks do occur in previously healthy individuals. It is not unusual for patients with *L. pneumonia* to be severely ill, as manifested by a high fever, rigors, and significant hypoxemia. This can occur even in a previously young and healthy patient. Failure to rapidly institute appropriate therapy in these cases is likely to result in a poor outcome, especially in older individuals. The greater severity of illness seen with *Legionella* distinguishes it from the other *atypical* pneumonias. For this and other reasons, classifying *atypical* pneumonias as a single entity can be misleading. In rare cases, Legionnaires' disease can be complicated by endocarditis, pericarditis, pancreatitis, skin abscesses, and rhabdomyolysis. A viral syndrome (Pontiac fever) is a nonpneumonic syndrome of Legionella infection.

Although important differences in severity and outcome exist, the clinical manifestations of Q fever, ornithosis, mycoplasmal pneumonia, *Legionella*, and *C. pneumoniae* infection can be similar and nonspecific. Appropriate exposure history should be sought and attention paid to illness in others with whom the patient may have been in contact, environmental exposures, and so on. Initial complaints can include coryza, pharyngitis, fever, headache, malaise, and, occasionally, chills. A bradycardia relative to high fever can occur in significant illness. Cough usually is present and may be nonproductive or associated with small amounts of mucoid sputum. Dyspnea is a prominent feature only when pneumonia is extensive. Pleuritic chest pain is rare, except in Q fever. Gastrointestinal symptoms, especially diarrhea, are a prominent finding in 20% to 40% of patients with Legionnaires' disease.

In all of these entities, the physical findings are often less impressive than would be predicted from the chest roentgenogram. Rales are usually present over involved areas, but findings of frank consolidation are uncommon. No diagnostic features on

the chest roentgenogram distinguish these infections from each other or from *typical* pneumonias; infiltrates can be unilateral, bilateral, patchy, or dense.

Routine laboratory tests also are nonspecific. Leukocytosis, which may be present or absent, is more common in Legionnaires' disease. Proteinuria may accompany high fever. In mycoplasmal infection, serologic abnormalities may appear, including rheumatoid factor, false-positive serologic tests for syphilis, and cold agglutinins (>50%). Occasionally, the latter occurs in titers high enough (≥1:500) to cause hemolysis. However, a rise in cold agglutinins is not specific for mycoplasmal disease and can be seen in up to 25% of viral pneumonias. Chlamydial infections and Q fever do not share with *Mycoplasma* organisms the proclivity for nonspecific antigenic stimulation. Legionnaires' disease is often associated with elevated liver enzymes, especially lactate dehydrogenase (LDH) levels greater than 700 U/ml, and hyponatremia (Na <130). In one study of community-acquired pneumonia, the combination of high fever (>39°C), hyponatremia (Na <130), high LDH (>700 U/ml), and central nervous system abnormalities was found to be predictive for the diagnosis of Legionnaires' disease.

A hallmark of all of these pneumonic illnesses is the absence of bacterial pathogens on Gram's stain and routine culture of clinical samples. Although specialized cultures, polymerase chain reaction PCR), and serologic tests for *atypical* organisms exist, their routine use is not recommended. These tests are generally expensive and of insufficient sensitivity and specificity. In addition, use of these tests is unlikely to alter patient management for two reasons. First, the antibiotics of choice are essentially the same for all of the organisms. Second, treatment decisions need to be made before (often weeks before) test results are available. Therefore, empiric therapy with one of the antibiotics described below is the recommended course.

Culture of *atypical* organisms is difficult. *Chlamydia* organisms and *Coxiella burnetii* are notorious causes of laboratory-acquired infection and, for this reason, are handled only in special laboratories. Isolation of *Chlamydia* species requires specialized tissue culture techniques and 4 to 5 days for detection of growth. *Mycoplasma* organisms can be handled safely in most laboratories, but their growth requires specialized cell-free media and 2 to 3 weeks of growth are necessary for detection. The culture of *Legionellae* is also not routine and requires special expertise. Other techniques, especially serologic testing, are most often used for establishing a diagnosis. A fourfold or greater rise in complement-fixing antibodies between acute and convalescent sera is considered definitively diagnostic for *Mycoplasma*, *Chlamydia*, *Coxiella burnetii*, and *Legionella*. PCR assays exist for *Mycoplasma*, *Chlamydia*, and *Legionella* organisms, but no US Food and Drug Administration-approved commercial test kits exist and such tests are available only through research and reference laboratories. Direct immunofluorescence can rapidly detect *Legionella* in sputum or lung tissue, although the sensitivity of this test is less than desirable (<75%). The *Legionella* urine antigen test is somewhat more reliable and can be positive for weeks following acute illness.

A decision to treat must be made before laboratory confirmation. The antibiotic options include (a) tetracyclines (tetracycline or doxycycline); (b) macrolides (erythromycin, clarithromycin, or azithromycin); or (c) newer fluoroquinolones (e.g., levofloxacin). These drugs are equally efficacious in *Mycoplasma* and *Chlamydia pneumonia*; however, tetracycline is clearly the drug of choice in *Coxiella burnetii* infections. Two to 3 weeks of treatment are recommended for tetracyclines or erythromycin. Use of newer antibiotics appears to allow shorter duration of therapy (clarithromycin: 10 days; azithromycin: 5 days; fluoroquinolones: 7 to 14 days). For *Legionella*, erythromycin is considered the drug of choice; it is initially given intravenously at high doses every 6 hours. Some suggest adding rifampin for patients who are severely ill. After the patient has improved sufficiently, oral medication can be substituted and continued for a total of 2 weeks. Macrolides and fluoroquinolones are preferred, but doxycycline is also effective. Azythromycin and levofloxacin are also available parenterally and can be considered for initial therapy in patients who tolerate erythromycin poorly. In fact, some experts prefer fluoroquinolones for the treatment of severely ill and immunocompromised patients.

In all but the most severe cases, complete healing of pneumonia is the rule. Radiographic resolution can be slow, but is usually complete by 6 to 8 weeks. Significant pulmonary tissue necrosis is rare in mycoplasmal disease but sometimes occurs in fulminant cases of Q fever and ornithosis.

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31. VIRAL PNEUMONIA

Bao Quoc Luu

Viruses have been estimated to cause approximately 8% of radiographically proved pneumonias in hospitalized adults and up to 49% in hospitalized infants. Because only a few patients presenting with symptoms of a viral illness warrant chest radiographs, these figures probably underestimate the true incidence of viral pneumonia. Interest in viral pneumonias has greatly increased in recent years because of several factors including (a) the increasing number of immunocompromised patients, stemming from both the acquired immunodeficiency syndrome (AIDS) epidemic and the growing popularity of organ transplantation; (b) the availability of new diagnostic techniques to detect viral infections; and (c) the development of effective preventative measures and antiviral therapies. In addition, the emergence of the hantavirus pulmonary syndrome, and the transmission of avian influenza viruses to humans during the Hong Kong flu epidemic in 1997 emphasized the important role that viruses play in human respiratory disease.

In the immunocompetent host, most viral respiratory infections have very similar clinical presentations. (The immunocompromised host is discussed in Chapter 101). The

diagnosis, therefore, depends heavily on the epidemiologic context, and on serologic and immunohistochemical data; recently developed cellular and molecular biology techniques may also help identify viral antigens and nucleic acids.

Influenza viruses remain the most common cause of pulmonary viral infections. They are RNA-containing viruses of the myxovirus family. Influenza viruses are divided into three groups (A, B, and C) on the basis of their internal membrane (M) and nucleoprotein (NP) antigens. Group A is further divided into a variety of antigenic subtypes based on two genetically distinct surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Hemagglutin is necessary for the process of binding to and penetrating the host cellular membrane. Neuraminidase aids in the release and spread of replicated viral particles. Influenza viruses can mutate spontaneously, producing new strains with changes in the H and N glycoproteins. The complete nomenclature of a strain of influenza virus includes the viral type (A, B, or C), the geographic location of discovery, the strain number, the year, and the H and N numbers (e.g. the A/Sydney/5/97/H3/N2). All three types (A, B, and C) can undergo minor structural changes; however, only type A can produce serologically distinct strains, designated by numerical subscripts in the H and N loci. Immunity to influenza infections depends on the host's production of antibodies to these glycoproteins. When a small antigenic change (*antigenic drift*) occurs, the effect on immunity is relatively minor. However, influenza is also capable of producing a major antigenic change (*antigenic shift*), resulting in devastating pandemic because of the lack of immunity in the population to the new antigen. The six deaths resulting from transmission of the avian H5N1 influenza virus to 18 humans in Hong Kong in 1997 was grim proof that avian influenza viruses could transmit to humans and cause severe infections. A growing body of literature supports the hypothesis that aquatic birds and animals (e.g., pigs) can be important reservoirs of influenza and perhaps even serve as *mixing vessels* for genetic recombination, leading to new, antigenically distinct and, thus, more virulent strains of virus.

Influenza infections occur in annual epidemics as well as in sporadic cases. In temperate zones, outbreaks occur in the winter; a seasonal association is less clear in tropical zones. Typically, patients present with fever, dry cough, myalgia, headache, conjunctivitis, and prostration. Gastrointestinal symptoms are seldom seen as are significant rhinorrhea and pharyngitis. Infections often exacerbate chronic illnesses such as chronic obstructive pulmonary (COPD) disease, asthma, and cystic fibrosis. Chest radiographs are often negative; however, in cases of pneumonia, infiltrates are usually patchy and bilateral. Bronchiolitis and peribronchial pneumonitis also occur and often present with segmental or subsegmental infiltrates. Most often, the infiltrates are self-limited and resolve within 3 weeks. Occasionally, the syndrome evolves into a diffuse pneumonia with bilateral infiltrates. Most cases of pneumonia occur during epidemics and pandemics. The risk of developing influenza pneumonia is increased in patients with chronic underlying illnesses such as mitral stenosis, COPD, cystic fibrosis, diabetes mellitus, and chronic renal failure. It is also increased in women during the third trimester of pregnancy.

Superinfection with bacteria such as *Staphylococcus aureus*, *S. pneumoniae*, and *Haemophilus influenza* can occur within 2 weeks (often within days) of influenza infection, and is a significant factor in the high mortality rates often seen during epidemics and pandemics. Recrudescence of fever and a productive cough of purulent sputum are important clinical signs of superinfection, especially in patients with predisposing factors. Chest radiographs show lobar or multilobar infiltrates. O leukocytosis with a left shift is seen. Sputum Gram's stain demonstrates many polymorphonuclear leukocytes and bacteria. The clinical course is determined in part by the specific bacterial pneumonia. However, complications such as abscess formation (especially with *S. aureus*), sepsis, empyema, and toxic shock syndrome have been reported.

Pathologically, the lungs of patients with fatal influenza infection without bacterial superinfection are dusky red to plum colored and are heavy and edematous. The airways are usually markedly congested and contain hemorrhagic fluid. Microscopically is seen diffuse alveolar damage with intraalveolar hemorrhage, capillary congestion, and variably severe interstitial mononuclear infiltrates. Often is seen type II cell hyperplasia and, characteristically, hyaline membranes. Neurologic sequelae of influenza, including Guillain-Barré syndrome, seizure, and transverse myelopathy, have been reported.

Severe myositis with elevated serum creatinine and phosphokinase levels has also been seen. Other rare complications include myoglobinuria, Reye's syndrome, thrombocytopenia, renal failure, myocarditis, and disseminated intravascular coagulopathy.

Influenza vaccination remains the most important preventive measure against the epidemic of influenza type A. It is recommended in late fall to early winter for patients with chronic cardiopulmonary disease, nursing home residents, persons aged more than 65 years, and any others wishing to offset the potential morbidity of an influenza infection. It is also recommended for people who may come in close contact with the high-risk population (e.g., household members of patients, medical personnel [physicians, nurses, and providers of home care], and community service workers [police and firefighters]). Amantadine and rimantadine are two effective therapeutic and chemoprophylactic agents against influenza A. They are not effective against influenza B. Their use has been limited because of the unpleasant central nervous system side effects, including insomnia, lightheadedness, difficulty concentrating, and irritability. Gastrointestinal side effects (e.g., nausea and upset stomach) have also been noted. The benefits and side effects of newer oral agents such as a selective neuraminidase inhibitor in preventing influenza infection are currently being studied. Treatment of influenza pneumonia is mainly supportive. Anecdotal reports suggest that high dose amantadine can be effective, but the optimal mode and duration of treatment has not been established. A combination of oral amantadine and aerosolized ribavirin has been suggested in patients at high risk who are hospitalized with influenza A pneumonia. Early diagnosis and treatment of superinfection with bacteria remain an important goal of treatment.

Respiratory syncytial virus (RSV) is an important cause of croup, bronchiolitis, and pneumonia in infants and young children. In adults, it typically causes an influenza-like illness with coryza, pharyngitis, and cough. It can lead to exacerbations of chronic illnesses (e.g., COPD and asthma). In the elderly, it causes a viral bronchopneumonia that can be complicated by a secondary bacterial pneumonia, as is the case with influenza. RSV can also cause nosocomial pneumonia. In immunosuppressed patients such as bone marrow transplant recipients, RSV pneumonia has a very high mortality rate. Treatment is mainly supportive. Aerosolized ribavirin has been associated with a reduction in viral titers, illness severity, and blood gas abnormalities. Bronchodilator and corticosteroid therapy has not been found to be beneficial.

Parainfluenza virus is an important cause of croup, rhinitis, pharyngitis, laryngitis, and bronchitis in children. In immunocompromised adults and children, parainfluenza virus can cause serious lung infections, including fatal pneumonia. In immunocompetent adults, it most commonly leads to exacerbations of chronic diseases and rarely causes pneumonia.

Adenovirus causes a particularly aggressive form of pneumonia in neonates, triggering necrotizing bronchiolitis and alveolitis. In large, closely quartered populations such as military recruits, it can cause viral pneumonias similar to other atypical pneumonias. In the general population, viral pneumonia is rarely seen; however, it is a common cause of pharyngitis, tracheobronchitis, and conjunctivitis. No specific treatment currently exists for adenovirus.

Varicella-Zoster virus (VZV) causes varicella, a highly contagious childhood exanthem with variable systemic symptoms. Reactivation of latent VZV infection results in herpes zoster. Epidemiologic evidence indicates that the virus is spread from person to person via airborne transmission. Nevertheless, in normal children, it is rarely associated with respiratory manifestation. In adults, viral pneumonia is a major complication of varicella. Symptoms include cough, fever, dyspnea, hemoptysis, and pleuritic chest pain (from herpetic vesicles on the pleural surface). Respiratory failure is fairly common. Radiographically, varicella pneumonia has a diffuse nodular (1–10 mm) pattern radiating from the hila, which may resolve into miliary calcified densities. Intravenous acyclovir, which is the treatment of choice, should be started early. Mortality rate is 10% to 15% and resolution generally coincides with clearing of the cutaneous vesiculopustular rash.

Measles (rubeola) is another highly contagious, systemic viral illness of childhood that can cause serious pneumonias in susceptible adults. As is the case in varicella, the respiratory tract serves as an important portal of entry. Unlike varicella, however, pulmonary infection is a common complication in older children and young adults. Pulmonary disease can be divided into three different forms: (a) primary measles pneumonia

(giant-cell interstitial pneumonia); (b) secondary bacterial pneumonia; and (c) atypical measles pneumonia. In one large series of military recruits with measles, 3.3% had clinical and radiographic evidence of pneumonia. One third of these patients had secondary bacterial pneumonia diagnosed via transtracheal aspirates. In a recent study of 75 civilians presenting to an emergency room with the clinical diagnosis of measles, 43 patients had abnormal radiographs and an (A-a) O_2 gradients of more than 30 mmHg. In fact, only 27 of the 43 had normal radiographs. In the 1970s, a variant form of measles was described in adolescents and young adults who received the inactivated measles vaccine between 1963 and 1968. Pulmonary abnormalities occurred in most cases, some with acute respiratory failure. Chest radiographs demonstrated patchy, diffuse, or dense lobar infiltrates; pleural effusions; and hilar adenopathy. This syndrome has not recurred since the use of inactivated measles vaccine was abandoned.

Cytomegalovirus (CMV) was discovered in 1956 to be the causative agent of severe infections in neonates. CMV has regained its notoriety recently as a common infecting agent of immunocompromised patients, especially organ transplant recipients and AIDS patients. Among immunocompetent children and adults, infection is most often asymptomatic, with perhaps fever as the only sign of infection. Some patients also have malaise, nonexudative pharyngitis, hepatosplenomegaly, lymphadenopathy, jaundice, and atypical lymphocytosis similar to that of infectious mononucleosis from Epstein-Barr virus. Following infection, however, immunocompetent hosts have a prolonged period of virus excretion in bodily fluid such as saliva, urine, stool, tear, breast milk, vaginal secretions, and semen. Thus, the reservoir for CMV is infected asymptomatic persons. The seroprevalence of CMV infection ranges from 40% to 100% in different parts of the world.

Reports have been made of CMV causing community-acquired viral pneumonia; however, the incidence has been low (0.9%) in a study of 443 such patients. In immunocompromised patients, such as organ transplant recipients, however, the virus causes a systemic infection and CMV pneumonia is a major cause of death in this population. Immunocompromised persons acquire CMV infection in one of three ways: (a) primary infection in seronegative patients; (b) reactivation in seropositive patients; or (c) re-infection from an exogenous source in seropositive patients. Co-infection with two distinct strains can occur simultaneously.

In the patient with pneumonia, the isolation of CMV from respiratory secretions, urine, or blood establishes that the patient has been infected by the virus, but does not determine with certainty whether CMV is responsible for the pneumonia. CMV pulmonary infection frequently occurs along with other pathogens such as *Pneumocystis carinii* (the most frequent), *Toxoplasma gondii*, *Aspergillus* species, *Norcardia asteroides*, herpes simplex viruses, and others. In addition, the clinical picture and radiographic pattern of CMV pneumonia in immunocompromised patients are nonspecific. Bronchoscopy with bronchoalveolar lavage can be used to exclude other causes, but the diagnosis of CMV pneumonia requires a biopsy specimen showing CMV in association with tissue damage. Newer techniques to diagnose CMV pneumonia such as immunofluorescence, immunohistochemical analysis, in situ hybridization, and polymerase chain reaction are under study.

Radiographically, CMV pneumonia often presents with a reticular pattern, but ground-glass opacities and parenchymal consolidation have also been described. Clinically, pneumonia can be mild or fulminant, progressing to acute respiratory distress syndrome (ARDS). Depending on the patient's immune status and severity of illness, treatment may require a combination of antiviral drugs (e.g., ganciclovir; or, alternatively, foscarnet) with intravenous immunoglobulin infusion. Among transplant recipients, the mortality rate from CMV pneumonia decreased from 90% to 50% with treatment. Vaccination of seronegative renal transplant patients with the Towne strain modified the severity of disease but did not decrease the rate of infection. In seropositive patients, no clear-cut benefit was seen.

Herpes simplex virus (HSV), type I, is transmitted via close contacts, through saliva or vesicle fluid, and is most commonly associated with gingivostomatitis. It is also often found as vesicular-ulcerative lesions in the lower respiratory tracts. Commonly, HSV-I causes tracheobronchitis in predisposed patients such as those with severe

burns, malignancies, AIDS, and organ transplants. Occasionally, it can also be found in nonimmunocompromised patients with recent myocardial infarcts or COPD and in elderly, but otherwise healthy, persons. Pneumonia is uncommon except in predisposed patients, where the disease spectrum ranges from an *innocent bystander* of other co-infections to fulminant disease with the development of ARDS. HSV-II rarely causes pulmonary infection except when it occurs as part of a systemic disease, usually via hematogenous dissemination. The definitive diagnosis of HSV pneumonia is often difficult. It depends on obtaining a sample of the involved lung for viral culture and testing for HSV antigen or nucleic acid. Lung involvement can be patchy; thus, numerous *generous* biopsy specimens should be obtained if possible to ensure sensitivity. The treatment of choice is intravenous acyclovir, with foscarnet being the alternative in cases of acyclovir-resistant HSV.

The *Hantavirus pulmonary syndrome* (HPS) is caused by the recently named *Sin Nombre* virus (SNV). Recognition of this syndrome came in May 1993 when a cluster of deaths occurred in residents of the Four Corners area of the southwestern United States. It is now known that SNV infects the common deer mouse *Peromyscus maniculatus* and that the disease is contracted when humans come in contact with the mouse's droppings. The outbreak in 1993 occurred after the atmospheric and oceanic conditions off the Pacific coast (*El Nino*) produced an unusually wet 1992 spring in the southwestern United States, leading to a population explosion of the deer mouse. In retrospect, tissue of patients who died of mysterious respiratory infections as far back as 1978 has been identified as containing SNV nucleic acids.

Patients with HPS present initially with a flulike illness characterized by fever, severe myalgia, cough, headache, and malaise. Unlike patients with other hantavirus syndromes characterized by hemorrhagic fever and renal failure, few patients have abdominal pain and back pain. Patients with HPS, develop rapid respiratory failure from noncardiogenic pulmonary edema caused by massive pulmonary capillary leaks. In patients intubated for respiratory failure, serous respiratory secretions high in protein and lactate dehydrogenase were found. Routine laboratory findings are nonspecific, but frequently include leukocytosis, with bandemia and especially with metamyelocytes in peripheral blood; increased hematocrit; thrombocytopenia; increased blood urea nitrogen and serum creatinine levels; decreased serum protein and albumin; elevated liver enzymes; increased prothrombin time and partial thromboplastin times; and lactic acidosis. Patients with fatal infection develop hypotension quickly. Early pulmonary artery catheter monitoring has demonstrated a hemodynamic profile different from that typically seen in septic shock. Instead of high cardiac output and low systemic vascular resistance, patients with HPS were observed to have a profound myocardial depressant effect with low cardiac index and low cardiac stroke volume, leading to low oxygen delivery. The combination of low cardiac index and elevated serum lactate level is a grave prognostic sign. Findings on chest radiographs include bilateral patchy infiltrates, interstitial infiltrates, or interstitial infiltrates with alveolar fillings. The pathologic findings include large, serous pleural effusions with severe edema of the lungs. Unlike other hantavirus syndromes characterized by hemorrhagic fever and renal failure, retroperitoneal effusions are not seen. Microscopically, lung tissue shows intraalveolar edema with scant to moderate numbers of hyaline membranes and scant to moderate numbers of interstitial lymphoid infiltrates. This is in contrast to the findings in ARDS, wherein is seen an intense infiltration of polymorphonuclear cells. No evidence was seen of viral cytopathic effect or viral inclusions.

The diagnosis should be suggested in previously healthy persons with the appropriate prodrome, recent exposure to mice, and rapid deterioration. The serodiagnosis of HPS requires the presence of antibodies against a panel of heterologous hantavirus antigens. Alternatively, tissue diagnosis can be made by testing for the presence of hantavirus RNA by reverse transcriptase polymerase chain reaction or immunohistochemical staining of formalin-fixed specimens. The mainstay of treatment is supportive critical care with mechanical ventilation, hemodynamic monitoring, and vasopressor agents, particularly dobutamine. The current mortality rate of HPS remains at approximately 76%. Ribavirin can be helpful, particularly during the prodrome phase before the onset of pulmonary edema, but this approach has yet to be tested in clinical trials.

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32. TUBERCULOSIS: EPIDEMIOLOGY AND PREVENTION

Philip A. LoBue

Tuberculosis is a pulmonary and systemic disease caused by the tubercle bacill *Mycobacterium tuberculosis*. It is spread by airborne transmission of droplet nu 1 to 5 μm in diameter. Transmission is only from person to person; fomites are involved. Several factors are significant in determining if transmission will oc (a) the number of viable bacilli in a patient's sputum and their concentration in air; (b) aerosolization of droplet nuclei by the patient coughing or talking; (c) susc tibility of the host; and (d) length of time the host is exposed to contaminated Even among household contacts of active tuberculosis patients, the risk of infect is surprisingly low; the United States Public Health Service (USPHS) reports approximate 28% incidence of infection in household contacts. In addition, ani and human studies have demonstrated that tuberculosis transmission dramatic decreases within days to weeks of instituting effective antimicrobial treatment, e in patients with floridly positive sputum.

Tuberculosis remains a significant worldwide public health problem. Approxima 33% of the world population is infected with the tubercle bacillus, and 3 million p ple die each year of tuberculosis. The human immunodeficiency virus (HIV) epide has dramatically altered tuberculosis epidemiology and is largely responsible f worldwide tuberculosis epidemic. Approximately 5.1 million people are infected w both tuberculosis and HIV. Recently, a *third epidemic* of multidrug-resistant tub culosis has developed. This epidemic has become a frightening reminder of the fail of public health programs worldwide to control tuberculosis.

In the United States, there had been a steady 4% to 7% annual decline in the case r until 1984. Between 1985 and 1992, however, the annual incidence of tubercul increased by 20% in the US population. This increase was concentrated in young p dominantly those aged 25 to 44 years), urban (especially New York, New Jersey, a California), racial and ethnic minority populations. The clustering was clearly lin to the high rates of HIV infection among these groups. A second epidemiologic tr emerged with increased emigration into the United States of persons from foreign co tries (especially Latin America, Southeast Asia, Africa, and eastern Europe); these p sons have made up increasingly larger proportions of active tuberculosis cases in United States. Before 1986, the foreign born accounted for 22% of tuberculosis cases. 1997, this number had increased to 39%. In some locations this phenomenon is e more pronounced. In San Diego, for example, nearly 70% of tuberculosis cases occu the foreign born. Because of extensive national and local control efforts, the annual i dence of tuberculosis has been on the decline again since 1992, falling 26% between 1 and 1997. Despite this welcome decline, the associations of this disease with conditi such as HIV infection, homelessness, intravenous drug use, and foreign birth remai

The tuberculin skin test (TST) is a major tool for investigating tuberculous in tion. It can be used diagnostically in the individual patient and epidemiologicall the general population. The skin test (Mantoux) is performed by the intracutane injection of a standardized, stabilized dose of 5 TU (tuberculin units) of purified p tein derivative (PPD). The extent of induration is measured 48 to 72 hours la Multiple puncture techniques (e.g., tine test) are less standardized and, therefore, recommended. The interpretation of the TST is based on an individual's epidemiol risk factors for tuberculosis infection. The 1994 American Thoracic Society (A'l Centers for Disease Control and Prevention (CDC) guidelines are as follows: (a) 5 r is considered positive for (i) individuals with HIV infection, (ii) close contact to

active tuberculosis case, or (iii) patients with a chest radiograph suggestive of old tuberculosis (fibronodular disease); (b) 10 mm is considered positive for (i) individuals of foreign birth from a high incidence country, (ii) those with underlying medical conditions such as diabetes, extended corticosteroid use, end-stage renal disease, intravenous drug use, immunosuppresive therapy, and malnutrition, or (iii) patients who reside in long-term facilities such as nursing homes or prisons; and (c) 15 mm is considered positive for all others. A positive skin test is considered to indicate the presence of infection with *M. tuberculosis*.

Conversion is defined as an increase in induration of 10 mm in individuals under age 35 years and 15 mm in individuals older than 35 years within a 2-year period. With old age, skin test sensitivity can wane. Repeated skin testing will help recall previous sensitivity, *the booster effect*. This is the rationale for recommending a *two-step skin-testing technique* in certain elderly patients. Two-step skin-testing is also suggested during the initial evaluation in periodic employee screening programs to avoid the problem of *false* conversions.

In many circumstances, the TST is neither sensitive nor specific for tuberculosis infection. Of patients with documented active tuberculosis, 10% to 25% will have a negative TST. The positive skin test is one manifestation of type IV delayed hypersensitivity. Clearly, certain biologic conditions, such as measles, acquired immunodeficiency syndrome, and other viral illness; Hodgkin's disease, sarcoidosis, uremia, and other debilitating illness; and certain drugs will suppress the type IV response and T-lymphocyte function. In addition, proper application of the skin test requires compulsive attention to technique and careful interpretation. TST should be performed by thoroughly experienced operators. Even under the best circumstances, a small percentage of patients will have an unexplained false-negative skin test finding; in vitro tests of T-lymphocyte function under development may help elucidate this perplexing phenomenon. Once infection occurs, tuberculin sensitivity is generally long lasting. False-positive test findings can occur for a number of reasons including cross-reactions caused by nontuberculous (atypical) mycobacteria infection.

Two methods have been used worldwide for tuberculosis prevention: bacille Calmette-Guérin (BCG) vaccination and isoniazid (INH) therapy for latent infection. BCG is a live, attenuated bacterial vaccine that has been evaluated extensively in worldwide trials. Except for occasional local reactions, its toxicity is minimal. In several controlled trials, the efficacy of case reduction has varied from 0 to 80%. In most trials, the incidence of miliary and meningeal tuberculosis has been greatly reduced. Variations in the efficacy of case reduction have been explained by vaccine potency variability and the differing incidence of infection with atypical mycobacteria, which seems to provide some *natural vaccination* against tuberculosis. A recent large trial conducted in India using a *very potent* BCG vaccine failed to show a protective effect against tuberculosis. BCG is best used in the noninfected (tuberculin-negative) population. The vaccine generally converts an individual's skin test to positive; however, the response has been somewhat variable among different vaccines and in different individuals and it correlates poorly with vaccine effectiveness. BCG obviously limits the diagnostic value of the tuberculin test. It has not been used in the United States because of the small percentage of cases that arise from new infections. It has been most useful in areas of the world where the case rate and new infection rate remain high.

The principal preventive tool in the United States has been treatment of latent infection with INH for 6 to 12 months. In the 1950s, when isoniazid became available as an inexpensive, bactericidal, and relatively nontoxic drug for the treatment of tuberculous disease, controlled trials were instituted to determine the efficacy of its prophylactic use. In more than 70,000 patients, the USPHS and others consistently demonstrated a 60% to 70% case reduction rate attributable to INH therapy. Follow-up for as long as 15 years confirmed the long-term protection INH bestows against tuberculosis. Unlike BCG, INH is appropriate for infected (i.e., skin test positive) persons, and is effective in preventing these individuals from developing active disease.

Initially, widespread isoniazid preventive therapy was predominantly restricted by economic considerations (i.e., the expense of treating millions of tuberculin reactors for 1 year). Certain priorities were established for groups at relatively high risk for developing tuberculosis. In recent years, the recognition of INH hepatotoxicity has modified the practice of preventive therapy.

Isoniazid-associated hepatitis is virtually indistinguishable clinically, chemically, and histologically from viral hepatitis. Prospective multicenter studies indicate that approximately 1% of patients given INH develop hepatitis. Among them is seen an approximate 10% mortality rate. The hepatotoxicity does not have the features of an allergic reaction and can occur at any time during therapy. Following transaminase levels does not reliably predict significant hepatocellular damage, because 10% to 20% of patients on INH develop transient minor elevations that disappear despite continuance of therapy. It is important to note that the incidence of isoniazid-associated hepatitis is directly related to age. It is rare in persons younger than 20 years and occurs in 0.3% between the ages of 20 to 34. However, the incidence rises to 1.2% between in those aged 35 to 49 and 2.3% for those aged more than 50 years.

Based on these data, the ATS issued recommendations that clinicians should balance the immediate and long-term risk of developing tuberculosis against the risk of isoniazid-induced hepatitis when determining the need for preventive therapy. In order of priority, INH should be used (a) in people recently infected (contacts, skin test converters, children); (b) in those with prior disease (abnormal radiographs) previously untreated; and (c) in other reactors aged less than 35 years. Isoniazid also is recommended for skin test-positive patients in certain special high-risk clinical situations such as acquired immunodeficiency syndrome, sarcoidosis, postgastrectomy, postpartum, chronic hemodialysis, and intestinal bypass surgery, and in those immunosuppressed by their disease or therapy, regardless of age. Isoniazid is not routinely recommended for those patients aged more than 35 years unless one of the above situations applies. The question of preventive therapy for pregnant women is a controversial one. The current American Thoracic Society recommendation is to defer isoniazid therapy until after delivery, unless the pregnant woman is likely to have been recently infected or has some other risk factor (e.g., HIV) for developing active disease. In that case, INH can be started immediately.

The USPHS has recommended that INH preventive therapy can be given for 6 months as an alternative to the 12-month program. This recommendation is based on studies indicating that most of the protective effect of INH is achieved in the first 6 months, although some additional benefit can be derived by extending the treatment to 12 months (a case reduction to 65% versus 75% in one study).

New guidelines have been developed to deal with HIV patients. All HIV-positive patients should have a tuberculin test. Tuberculin reactors (≥5 mm) have the highest priority for INH therapy. Selected HIV-positive, tuberculin-negative individuals should receive INH prophylaxis—those with history of previous positive skin test, exposure to active tuberculosis, or radiologic findings suggestive of old tuberculosis (but only after active tuberculosis has been excluded). Isoniazid prophylaxis should last for 12 months. Several recent studies done in HIV-positive patients suggest that the combination of daily rifampin and pyrazinamide for 2 months is equally efficacious in the prevention of tuberculosis when compared with INH. In its most recent guidelines for tuberculosis treatment for HIV-positive patients, the CDC lists 2 months of rifampin and pyrazinamide as an acceptable alternative for preventive therapy. It is important to note that rifampin should not be used in patients taking protease inhibitors and non-nucleoside reverse transcriptase inhibitors, but that rifabutin can be considered as an alternative to rifampin with certain protease inhibitors.

Exposure to drug-resistant disease is a difficult problem with regard to preventive therapy. For isoniazid-resistant, rifampin-sensitive exposures, rifampin can be used. For multidrug-resistant tuberculosis exposure, some have suggested the use of pyrazinamide or ethambutol in combination with a fluoroquinolone. Good data are not available, however.

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33. TUBERCULOSIS: SYNDROMES

Philip A. LoBue

Tuberculosis, one of the *great imitators* in clinical medicine, has protean clinical manifestations that can be divided into pulmonary and extrapulmonary syndromes.

The initial portal of entry of the tubercle bacillus is almost always the lung. The inhaled droplet nuclei usually lodge in the middle or lower lung zones where regional ventilation is greatest, resulting in a local inflammatory reaction with spread to regional lymph nodes and subsequent hematogenous dissemination. Distant organs, especially the kidneys, bone, central nervous system, as well as the lung apices, are seeded, but overt clinical disease of these areas rarely occurs. A low-grade fever and symptoms of an upper respiratory illness may also be present. The chest roentgenogram may show a small area of pneumonitis and, often, hilar and paratracheal lymphadenopathy. Prominent hilar adenopathy is frequent in children; it occurs less commonly in adults.

The initial infection termed *primary tuberculosis*, resolves spontaneously in most individuals. Remnants of such *healed* lesions appear on chest roentgenogram as calcified parenchymal nodules (Ghon's lesions) and are often associated with calcified hilar lymph nodes (Ranke's complex). In a small percentage of individuals, the initial infection progresses and can manifest as (a) rupture of subpleural infectious foci into the pleural space, resulting in tuberculous pleurisy; (b) extensive caseous pneumonia; (c) enlargement of tuberculous lymph nodes, resulting in bronchial obstruction (collapse-consolidation lesion); (d) rupture of a tuberculous focus into a bronchus, leading to extensive endobronchial spread throughout one or both lungs; and/or (e) rupture of a tuberculous focus into a pulmonary blood vessel with hematogenous spread resulting in acute disseminated disease.

Tuberculous disease can reappear months to years after containment of the initial infection. The factors causing the *breakdown* of previously *healed* lesions are poorly understood. Certain conditions appear to predispose to reactivation (or spread) of a tuberculous infection, including malnutrition, alcoholism, poorly controlled diabetes mellitus, silicosis, immunosuppression (by disease processes or drugs), the postpartum period, gastrectomy, chronic hemodialysis, and jejunoileal bypass surgery. In most patients, however, no predisposing factor can be identified.

Reactivation or postprimary pulmonary tuberculosis usually presents as an infiltrate in the apical and posterior segments of the upper lobes. The patient can be entirely asymptomatic or have nonspecific symptoms of chronic respiratory infection (e.g., fever, weight loss, productive cough, and hemoptysis). The chest roentgenogram may reveal a somewhat nondescript fibronodular or fluffy alveolar-filling process in the upper lung fields, but frequently shows cavity formation, fibrosis with volume loss, or both. The process occasionally heals spontaneously but more frequently progresses locally in the absence of drug therapy. Advanced disease, rarely, can be associated with rupture of a hypertrophied pulmonary artery (Rasmussen's aneurysm) into a cavity, resulting in massive hemoptysis. Occasionally, is seen rapid progression of pulmonary disease with severe ventilation-perfusion ($\dot{V}/\dot{Q}$) disturbances that can present as the adult respiratory distress syndrome. New hematogenous dissemination and extrapulmonary disease can occur during progressive pulmonary tuberculosis.

Routine laboratory studies in pulmonary tuberculosis are nonspecific. Hematologic studies often reveal a mild anemia, leukopenia, or a monocytosis, but such extremes as pancytopenia or profound leukocytosis (leukemoid reaction) also occur. Hyponatremia, usually attributable to the syndrome of inappropriate antidiuretic hormone production,

occurs in more than 10% of patients with pulmonary tuberculosis. Addison's disease is a very rare cause of hyponatremia in patients with tuberculosis.

The definitive diagnosis of pulmonary tuberculosis depends on obtaining a positive culture of infected material. If cultures are negative or obtaining a culture is not possible, a presumptive diagnosis can be made from clinical inference and therapeutic trial. The tuberculin skin test provides information as to whether a tuberculous infection is present but does not distinguish between active disease and inactive infection. A typical chest radiograph is helpful, but nonspecific: a variety of nontuberculous processes can have a similar appearance. Spontaneous early-morning sputum samples or, if necessary, aerosol-induced sputa have replaced analysis of gastric washings as the methods of choice for bacteriologic assessment. Initially, the specimens are stained by the Ziehl-Neelsen's or fluorescent techniques, or both. When sputum analyses are unfruitful, bronchoscopy with brushings, transbronchial biopsy, or needle aspiration can provide diagnostic material. Such approaches can enhance both the speed of diagnosis and the overall diagnostic yield. In addition to histologic examination for caseating or noncaseating granuloma, all tissue specimens should be cultured for mycobacteria. Cultures are also essential for all specimens, because (a) smears alone will miss up to 50% of active tuberculosis cases and (b) mycobacteria other than *Mycobacterium tuberculosis* can yield positive smears. Special culture media are required, and the laboratory should have proficiency in mycobacterial techniques. Cultures may later prove invaluable in providing drug sensitivity information to aid in the management of a *treatment failure*.

One of the major limitations of the culture technique in the past was that 6 to 8 weeks were required to obtain results. Newer laboratory diagnostic techniques have proved very useful in the management of mycobacterial diseases. The BACTEC™ (Becton Dickinson, Sparks, Maryland) system is a rapid radiometric culture technique useful with clinical specimens. Mycobacterial growth can be detected in as few as 5 to 8 days, although on average it takes 3 to 4 weeks. Deoxyribonucleic acid (DNA) probe technology can provide a very rapid (hours) method of differentiating *M. tuberculosis* complex from nontuberculous mycobacteria in growing cultures. This technique has proved to be highly specific and sensitive. The newest laboratory tools for the diagnosis of tuberculosis are the nucleic acid amplification (NAA) tests. Two commercially available NAA tests have been approved by the Food and Drug Administration (FDA) for use on acid fast bacillus (AFB) smear-positive respiratory specimens, the polymerase chain reaction and transcription mediated amplification. NAA tests can be performed in 6 to 8 hours. The combination of a positive AFB smear and positive NAA test is essentially diagnostic of active tuberculosis. A negative NAA test in the face of a positive AFB smear suggests that the patient has infection with nontuberculous mycobacteria. NAA tests are also approximately 25% more sensitive than the AFB smear and can be of use when the smear is negative and the clinical suspicion for tuberculosis remains moderate or high. It is anticipated that these tests will be FDA approved for use on smear-negative specimens in the near future. There is less experience with the use of NAA tests for nonrespiratory specimens. Several studies suggest they can be useful for the diagnosis of extrapulmonary tuberculosis, especially for meningitis. The finding of a positive NAA test does not obviate the need for cultures, as NAA tests do not give any information about drug susceptibilities.

Extrapulmonary tuberculosis can occur with or without concurrent active pulmonary tuberculosis. Most frequently, the pathogenesis is that of recrudescence of a previously quiescent hematogenous lesion. However, upper airway and laryngeal disease, lymphatic tuberculosis, and pleural or pericardial tuberculosis commonly arise by extension from contiguous structures. Gastrointestinal tuberculosis can follow ingestion of expectorated infectious sputum.

Pleural tuberculosis usually presents as a unilateral, exudative, predominantly lymphocytic, pleural effusion often associated with ipsilateral pulmonary tuberculosis. Symptomatic improvement often occurs spontaneously. With thoracentesis and pleural biopsy, the tuberculous cause can be documented in 80% to 90% of cases. High levels of adenosine deaminase and interferon gamma in the pleural fluid have been associated with pleural tuberculosis in several studies. Younger patients with an *idiopathic* pleural effusion and a positive tuberculin reaction are often managed as pleural tuberculosis cases on clinical grounds. However, multiple closed pleural biopsies or surgical pleural

exploration should be strongly considered when resolution is not prompt. Pericardial tuberculosis can present with clinical features of tamponade or chronic constrictive pericarditis. Pericardial involvement should be considered in all tuberculous patients with cardiomegaly or unexplained *heart failure* or arrhythmias. A calcified pericardium on chest roentgenogram strongly suggests the diagnosis. Echocardiography may demonstrate the presence of pericardial fluid; however, pericardiocentesis and possibly pericardiectomy are necessary to confirm the diagnosis. Cultures of pericardial fluid are positive in only 50% of cases.

Large airway (endobronchial) and laryngeal tuberculosis can be present with a normal chest x-ray study, but are usually associated with extensive cavitary pulmonary disease. Hoarseness is a common presenting symptom. Classically, laryngeal tuberculosis has been considered extremely infectious. A recent report suggests that it is not the laryngeal disease *per se* but the often-associated extensive pulmonary disease that is responsible for the contagiousness.

Disseminated (miliary) tuberculosis is being seen in adults much more commonly than in past years. Skin anergy can be present, but most recent studies report tuberculin positivity in 60% to 90% of patients. Sputum smears and cultures can be positive in 30% to 60% of patients. Extrapulmonary sources of culture material (e.g., liver biopsy, bone marrow biopsy, and urine) should be obtained if the diagnosis is considered. The mortality rate is 5% to 15% with chemotherapy.

Tuberculous meningitis usually results from acute hematogenous spread and is present in up to 33% of cases of miliary disease. Rarely, it can result from breakdown in a *silent* granuloma or residua from remote hematogenous dissemination and, in children, by direct spread from a tuberculous otitis. Meningitis can present insidiously with lethargy, confusion, and headache. The cerebrospinal fluid (CSF) often shows a lymphocytic pleocytosis, a glucose less than 20 mg/dl, and a markedly elevated protein level. The CSF smear is positive in only 20% of the cases, whereas cultures are positive in 75%. Pathologically, an occlusive cranial arteritis can lead to infarction, cranial nerve palsies, and hydrocephalus.

Genitourinary tuberculosis classically presents as *painless hematuria* and *sterile pyuria*, but dysuria and secondary bacterial infection are not infrequent. Of all tuberculosis patients, 5% to 7% may have positive urine cultures for *M. tuberculosis*, despite the absence of urinary symptoms and normal urinalyses. The renal parenchyma, caliceal system, ureters, and bladder can all be affected. If renal tuberculosis is suspected, early-morning urine cultures, an intravenous pyelogram, and, possibly, cystoscopy are indicated. Frequently, associated epididymal or testicular disease exists, which can lead to sterility.

Bone and joint tuberculosis can be difficult to diagnose in the early stages of disease. Pain and joint swelling can occur, and there may be paraosseus (*cold*) abscesses and sinus tract formation. The weight-bearing bones and joints are most commonly affected, especially the spine (Pott's disease), hips, and knees. Early diagnosis by joint aspiration and biopsy is essential to prevent significant disability and to avoid the need for surgery.

New clinical syndromes of tuberculosis have been identified in patients with acquired immunodeficiency syndrome (AIDS). Patients with one infection should be tested for the other. *Atypical* features of tuberculosis found in AIDS patients include (a) higher frequency of negative tuberculin tests (61% vs. 9%); (b) higher frequency of extrapulmonary sites (60% vs. 28%); (c) higher frequency of diffuse or miliary infiltrates (60% vs. 32%); (d) higher frequency of hilar adenopathy (20% vs. 0%); (e) lower frequency of focal infiltrates (35% vs. 68%); and (f) lower frequency of cavities (18% vs. 67%). Patients infected with the human immunodeficiency virus (HIV) are much more likely to develop infection after exposure to tuberculosis and to develop rapidly progressive, often fatal disease.

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34. TUBERCULOSIS: TREATMENT

Philip A. LoBue

Although the principles of effective antituberculous chemotherapy are not difficult or complex, even well-trained physicians, at times, inappropriately treat tuberculosis patients. This problem most likely reflects the relatively limited exposure that many physicians have had to this disease. As a consequence, local health departments have assumed a greater role in the management of active tuberculosis cases. In many areas, health departments assume direct responsibility for the treatment of tuberculosis patients and monitor treatment provided by community physicians.

The treatment of tuberculosis involves the administration of appropriate drugs in specific doses, combinations, and durations. Furthermore, successful therapy requires that the patient comply with the prescribed regimen. Surgery is rarely necessary except in selected cases of multidrug-resistant tuberculosis and for complications of tuberculosis such as (a) emergency treatment of massive hemoptysis; (b) therapy of bronchopleural fistulas; or (c) for relief of *mechanical* problems in skeletal tuberculosis.

Since the first antituberculous medications were developed in the late 1940s, the standard regimen for the treatment of tuberculosis has undergone considerable change in the specific drugs used, the dose schedules, and the duration of therapy. Although clinical investigations are ongoing and individual patients or situations can require tailored regimens, the combination of isoniazid (INH), rifampin, and pyrazinamide (PZA) has emerged as the mainstay of treatment of patients with sensitive organisms. Other drugs, however, especially ethambutol and streptomycin, still have important roles in certain contexts and are discussed later in this chapter.

For patients with active tuberculosis that is known to be sensitive to INH and rifampin, standard chemotherapy consists of INH, rifampin, and PZA daily for 2 months, followed by daily INH and rifampin for 4 months. INH and rifampin can also be given twice weekly or thrice weekly instead of daily during the last 4 months of therapy. If this is done, higher doses of INH are required and it is recommended that intermittent therapy be done as directly observed therapy (DOT) (see below). Daily INH and rifampin can be used without PZA for treatment of sensitive tuberculosis, but therapy should be extended to 9 months. In geographic locations where INH resistance is known to be 4% or greater, ethambutol or streptomycin should be started in addition to INH, rifampin, and PZA while awaiting sensitivity testing. Once the organism is known to be susceptible to INH and rifampin, the ethambutol or streptomycin can be discontinued. If initial therapy includes four drugs (e.g. INH, rifampin, PZA, and either ethambutol or streptomycin), the frequency of medication can be decreased to twice weekly after 2 weeks of daily therapy (Denver regimen). If this is done, all four drugs should be continued for the first 2 months of therapy; INH, ethambutol, and PZA must be given at higher doses, and DOT is recommended.

Patients infected with organisms that are resistant to INH, rifampin, or both, require modifications in their drug regimens. For tuberculosis that is INH resistant, the two

recommended regimens are daily rifampin, ethambutol, and PZA for 6 to 9 months or, alternatively, daily rifampin and ethambutol for 12 months. For tuberculosis resistant to rifampin, the recommended therapy is INH and ethambutol for 18 months. Tuberculosis that is resistant to INH and rifampin is termed *multidrug resistant* (MDR). Treatment of MDR tuberculosis is often complex and should be done with the consultation of a tuberculosis expert. MDR tuberculosis should be treated with at least two (but preferably three or more) medications to which the organism is susceptible. Therapy should continue for at least 18 to 24 months after cultures have converted to negative. Surgical resection of heavily diseased areas of the lung is frequently used as an adjunctive therapy for MDR tuberculosis and should be considered in suitable candidates.

Since the 1990s, use of DOT by local health departments has become a major tool in tuberculosis control and treatment. With DOT, some or all doses of medication are taken in the presence of a nurse or other ancillary healthcare worker. This can be done by having the patient come to the clinic or by sending an outreach worker to the patient's home. This technique is very resource intensive, but still can be cost-effective if treatment failures because of noncompliance can be minimized. Priority for DOT is usually given to children, individuals with drug-resistant disease, and those who are likely to be noncompliant (intravenous drug users, those with psychiatric disorders, the homeless, and so on).

The principles of tuberculosis management are similar in pregnant and nonpregnant patients, with a few notable exceptions. Isoniazid, ethambutol, and rifampin have been used successfully and safely. Streptomycin has caused a somewhat greater frequency of eighth cranial nerve damage to the fetus and probably should not be used. Pyrazinamide has not been shown to be teratogenic, but there is insufficient experience with this drug in pregnancy to assure its safety; its use during pregnancy is not recommended. The same can be said for all second line drugs, which are not considered safe in pregnancy.

Tuberculosis in children is treated similarly to adult disease. In the past, concern was expressed about the use of ethambutol in very young children because of the difficulty in screening for retrobulbar neuritis. More recent data, however, suggest that ethambutol is safe in this population.

The response to antituberculous therapy is usually rapid. The number of acid-fast bacilli found on smears typically declines within 2 weeks. Approximately 50% of patients have negative smears and cultures after 2 months; 75% after 4 months; and more than 95% after 6 months. Occasionally, a patient who is otherwise doing well will have a positive sputum late in the course of therapy. This is not necessarily a treatment failure. When deciding if a new regimen is required, several factors including clinical course, chest radiographs, and bacteriologic data must be taken into account.

The possibility of drug resistance should be considered because of the direct relationship between drug resistance and treatment failure. Until recently, the incidence of primary drug resistance was low (3.5%) and stable; however, the situation has changed dramatically. Although significant geographic variation in drug resistance is seen, the incidence of resistance is growing nationwide. Current recommendations for initial tuberculosis therapy, therefore, include (a) initial drug susceptibility studies for all positive cultures; (b) initial four-drug therapy for all patients, except in areas where INH resistance is very low (<4%); and (c) initial DOT for most patients. If drug resistance is demonstrated, the therapeutic regimen should be altered as described above. Factors influencing the likelihood of drug resistance include (a) history of previous antituberculous therapy; (b) country of origin (especially Southeast Asia and Latin America); and (c) duration of residence in North America.

Occasionally, because of lack of patient compliance, drug resistance, or a previous inadequate drug regimen, one must design a retreatment program. Although few *hard* data are available concerning successful retreatment regimens, experienced clinicians agree about the general principles. Retreatment regimens should be based on in vitro sensitivity testing as described above. In vitro sensitivity testing should be repeated on the most recent positive culture. If this is not available at the time of initiation of therapy, a decision regarding drug therapy should be based on the patient's past drug history. Drugs the patient has received previously should not be a mainstay of the *new* regimen. The new regimen should include at least two new drugs that the patient has not taken before and to which the organism is presumed to be sensitive. Most physi-

cians recommend at least three new drugs. A cardinal rule is that new drugs should never be introduced sequentially (one at a time) to a failing regimen. If the retreatment regimen proves successful (sputum becomes culture-negative), therapy duration should be based on the most recent sensitivity results as described above.

The initial treatment for patients with the acquired immunodeficiency syndrome is the same as in human immunodeficiency virus (HIV)-negative individuals: isoniazid, rifampin (or rifabutin), and pyrazinamide (along with ethambutol or streptomycin in areas with INH resistance of 4% or greater). Rifampin, however, should not be used in patients on protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI). For this reason, consideration should be given to substituting rifabutin (a comparably effective rifamycin) for rifampin. Rifabutin can be used with some protein inhibitors (indinavir, nelfinavir) and possibly with one NNRTI (efavirenz) if appropriate dosage adjustments are made. Because of the complex drug interactions between many antiretroviral medications and rifabutin, it is strongly recommended that tuberculosis treatment of patients on such drugs be carried out in consultation with an HIV expert.

For drug-susceptible disease, some controversy exists regarding adequate duration of therapy. Most HIV-tuberculosis experts believe that the standard 6-month short course therapy is adequate (assuming an appropriate clinical and microbiologic response). This is based on recent studies demonstrating equivalent efficacy between 6-month therapy and longer regimens. Others believe these data are insufficient to refute previous trials suggesting that longer therapy was superior, and they recommend 9 to 12 months of treatment. The official Centers for Disease Control and Prevention statement recommends at least 6 months of therapy with extended treatment for patients with a delayed response to therapy. If INH or rifampin resistance is present, therapy should be the same as for those patients without HIV, again with consideration to extending therapy duration for those patients with a delayed response.

In recent years, it has been noted that a temporary exacerbation of tuberculosis symptoms and lesions can occur in patients with HIV who are taking antiretroviral therapy. This phenomenon, known as the *paradoxical reaction*, has been attributed to recovery of the delayed hypersensitivity response in these patients and increased exposure to tuberculosis antigens following the initiation of bactericidal antituberculosis therapy. In general, modifications of tuberculosis therapy and antiretroviral therapy are not necessary and a short course of corticosteroids may ameliorate symptoms associated with this reaction.

Drugs used in tuberculous therapy can be divided into *first-line* and *second-line* agents. The first-line drugs consist of isoniazid, ethambutol, rifampin, pyrazinamide, and streptomycin. The first-line drugs are the most effective and least toxic. INH is an effective bactericidal drug. Its major adverse reactions are hepatitis and neuritis. Ethambutol is a bacteriostatic agent that has been in general use for over two decades. It is approximately as efficacious as para-aminosalicylic acid (PAS). A dose of 25 mg/kg daily is used for 2 to 3 months and then decreased to 15 mg/kg. Retrobulbar optic neuritis has occasionally complicated therapy with doses in excess of 20 mg/kg for prolonged periods, but is very rarely seen when using 15 mg/kg. Rifampin is a relatively nontoxic bactericidal drug. The major side effects are hepatotoxicity and hypersensitivity reactions. Some evidence suggests that the combination of rifampin and isoniazid can be associated with a greater incidence of hepatitis than either drug alone. Hypersensitivity reactions, including a flulike syndrome, thrombocytopenia, and, rarely, acute renal failure, most commonly occur with high-dose intermittent therapy. Rifampin increases hepatic metabolism of some drugs, causing important drug interactions. Oral contraceptives can be ineffective at normal doses because their hepatic metabolism is increased. In addition, rifampin can induce methadone withdrawal. Pyrazinamide is now used as part of initial treatment regimens in 6-month chemotherapy programs. Its principal side effects are hepatotoxicity and hyperuricemia; the latter rarely leads to gout or renal failure. Several aminoglycoside antibiotics are of proven efficacy in therapy of tuberculosis. Unfortunately, they all require intramuscular administration and have a high incidence of serious side effects. Streptomycin, the first drug available for tuberculosis therapy, is still occasionally used as a first-line drug; however, its value is limited by dose-related renal and eighth cranial nerve toxicities. Other aminoglycosides such as capreomycin,

kanamycin, and amikacin have similar toxicities and may be slightly less effective. They are generally reserved for MDR tuberculosis. If one of the aminoglycosides is required, streptomycin should be the first choice, followed by capreomycin, kanamycin, and amikacin. PAS, ethionamide, and cycloserine are oral preparations that are usually used only in MDR tuberculosis. PAS and ethionamide cause severe gastrointestinal distress, whereas cycloserine is associated with personality changes, depression, frank psychoses, and, in high doses, seizures.

A better understanding of the interaction of drugs with the various mycobacterial populations (rapidly growing, intermittently growing, dormant) can lead to the development of newer, safer, more effective antituberculous drugs. The quinolones (ciprofloxacin, ofloxacin, and especially levofloxacin) have shown in vitro and clinical efficacy. Because these drugs are generally well tolerated, they are rapidly becoming a mainstay of MDR treatment regimens.

Drug reactions can occur during initial treatment or during retreatment. Often difficult to diagnose, they can be confused with manifestations of tuberculosis or intercurrent disease. Sometimes drug reactions are relatively mild so that stopping therapy is not warranted. Specific reactions can be handled by discontinuing the suspect drug. Often drugs have overlapping toxicity, and reactions are nonspecific (e.g., fever, rash, jaundice). In such cases, all drugs should be stopped for a brief period (1 week) and then reintroduced singly, the least likely offender first. Some clinicians re-initiate drugs at low doses, whereas others resume full-dose therapy. If a reaction appears a second time, then another drug will have to be substituted. (One drug can be added to a successful regimen.)

Chemotherapy for extrapulmonary tuberculosis does not differ in principle from that outlined above. Isoniazid, ethambutol, and rifampin penetrate the blood–brain barrier and are useful in central nervous system tuberculosis. Duration of therapy is the same as for pulmonary disease, with the exceptions of (a) meningitis in children; (b) bone and joint disease; and (c) miliary tuberculosis. For these conditions, it is recommended that treatment be extended to 12 months. Spinal stabilization procedures can benefit selected individuals with Pott's disease. Corticosteroids should be used routinely for the treatment of tuberculous meningitis in children. The use of corticosteroids for tuberculous meningitis in adults is more controversial. Corticosteroid treatment is generally recommended in adults with advanced disease, especially in cases of obtundation or coma. Some experts use corticosteroids routinely in adult cases because current evidence suggests that essentially no danger exists of a significant adverse effect as long as the diagnosis is well established and appropriate antituberculous therapy has been initiated. On the other hand, no good evidence is found that use of corticosteroid therapy decreases the likelihood of long-term neurologic sequelae in adults.

Corticosteroid therapy can be useful also in the early management of tuberculous pericarditis. In extensive pulmonary tuberculosis, several studies have shown that steroid-treated patients achieve more rapid defervescence, symptomatic improvement, and radiologic clearing. No long-term benefits have been demonstrated, however, and steroids are not generally recommended as adjunctive therapy for pulmonary tuberculosis.

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35. MYCOBACTERIAL INFECTION DUE TO MYCOBACTERIA OTHER THAN TUBERCULOSIS (MOTT)

Antonino Catanzaro

Mycobacterial infections caused by mycobacteria other than tuberculosis (MOTT) encompass a variety of acid-fast bacilli that are biologically distinct from *Mycobacterium tuberculosis*, *M. leprae*, and *M. bovis*. They were long considered saprophytes or culture contaminants, and their significance as human pathogens, with the potential to cause disease in virtually any organ in the body, has only recently been recognized.

The distribution of these organisms is worldwide, although important regional predominances of certain species appear to exist. For example, *M. kansasii* is commonly found in Texas, Illinois, and California and among urban more than rural inhabitants; and *Mycobacterium avium-intracellulare* complex (MAC; also known as MAI) is more common in the southeastern states among rural inhabitants. Formerly, MAC was called *Battey-type bacillus*, named for the Georgia institution where it was first recognized to cause a disease clinically similar to pulmonary tuberculosis.

The MOTT are widely dispersed in the environment and commonly isolated in many communities from soil, water, rivers, and milk. Diagnosis of disease caused by MOTT is complicated by the fact that most of these organisms generally behave as saprophytes and are frequently isolated from sputum of presumably noninfected individuals, particularly those with chronic lung disease. Skin testing with homologous antigens contributes little to the diagnosis of MOTT disease, because of its many shortcomings such as cross-reactivity, frequent inapparent infection, and lack of availability of antigens. Diagnosis, therefore, requires repeated isolation of a given species, a compatible clinical and roentgenographic picture, as well as exclusion of other potential causative agents. Repeated isolation of *M. kansasii*, however, is probably unnecessary to establish the presence of infection, because it rarely occurs as a saprophyte.

Recent advances have been made in the ability to detect and identify mycobacteria, which greatly reduce the time in which results are available. Two popular methods of rapid detection include BACTEC TB and Septic-Chek AFB systems (both from Becton Dickinson, Sparks, Maryland). Another available method utilizes chemiluminescent DNA probes.

Pulmonary infection with MOTT, which is most often caused by MAC or *M. kansasii*, is similar in many respects to classic tuberculosis. Rarely, pulmonary infections can be caused by *M. szulgai*, *M. xenopi*, *M. fortuitum*, or *M. chelonei*. In general, constitutional symptoms are less severe and the course more indolent than in classic tuberculosis. Pulmonary infection with MOTT is more prevalent among individuals with preexistent bronchopulmonary disorders such as bronchiectasis, chronic obstructive pulmonary disease, silicosis, or healed pulmonary tuberculosis. Antecedent spontaneous pneumothorax is said to occur in up to 33% of patients who develop *M. kansasii* disease, which is much more frequent than in classic tuberculosis. Pleural effusions are rare.

Lymphadenitis caused by MOTT is found almost exclusively in children. The causative organism is usually MAC but can be *M. kansasii*, Lymphadenitis caused by *M. scrofulaceum* has diminished greatly in frequency in recent years. Infection presumably results from an inapparent breach of the tonsillar mucosa. Patients most frequently present with asymptomatic, unilateral, anterior cervical adenopathy. Less commonly, other nodes can be involved; in advanced cases, draining sinuses and fistulae may appear. The chest x-ray study is often clear.

Swimming pool granuloma (*M. marinum*) is a superficial cutaneous ulceration that usually presents on the extremities. Healing generally occurs spontaneously, although complete resolution can take 3 to 4 months. However, treatment may be needed in selected cases, particularly when resolution is indolent. In contrast, *M. ulcerans* can produce extensive tissue necrosis (Buruli or Bairnsdale ulcer) requiring surgical debridement and skin grafting. Subcutaneous abscesses caused by *M. fortuitum* can result from inoculation with contaminated surgical implements.

Well-documented infections involving bone, joints, urinary tract, and meninges have been reported with a variety of nontuberculous organisms. Widely disseminated dis-

ease can occur, especially in immunosuppressed individuals and in those with hematologic abnormalities. MAC disseminated infection has been a major clinical problem in patients with acquired immunodeficiency syndrome (AIDS).

The proper approach to management of pulmonary disease caused by nontuberculous mycobacteria depends primarily on the causative species. It is important to stress that, because no documentation of communicability exists, the standard measures for reducing communicability used in patients with *M. tuberculosis* are not necessary. In fact, health departments typically do not follow these cases.

Mycobacterium kansasii responds well to chemotherapy. In vitro susceptibility studies do not necessarily correlate with in vivo drug efficacy. The initial regimen should include isoniazid, ethambutol, and, most importantly, rifampin. Rarely, regimens including four or five drugs are necessary to affect a bacteriologic cure. Medication should be continued for at least 1 year after the patient is sputum culture-negative and for a minimum of 2 years. More than 90% success has been achieved with drug therapy alone. Adjunctive surgery is rarely indicated except in well-localized disease that has responded poorly to adequate chemotherapy. Surgery may be necessary in patients who have demonstrated an inability or unwillingness to take chemotherapy.

The diagnosis and treatment of disease caused by MAC is much more complicated. Although the American Thoracic Society recently concluded that a single sputum examination might suffice to establish the diagnosis in a patient with a compatible presentation, the issue is complex and controversial. It is recommended that the decision to initiate therapy for MAC be individualized according the certainty of the diagnosis and the clinical characteristics of the patient. For example, patients who have bronchiectasis can become colonized with MAC; these patients may respond to broad-spectrum antibacterial medications and pulmonary toilet without specific treatment for MAC.

Mycobacterium avium-intracellulare shows in vitro resistance to most antituberculous drugs, but no controlled clinical trials are available to determine clinical outcomes for various drug regimens. A four-drug regimen that includes clarithromycin produced a sputum conversion rate of 71.8% in a study of 39 immunocompetent patients who received 6 or more months of therapy. This regimen, which included clarithromycin, ethambutol, rifampin, and initial kanamycin and subsequent quinolone benefited newly treated patients, but re-treated patients had problems such as adverse side effects and low sputum conversion rates. Patients from whom MAC is sporadically recovered and who have no pulmonary disease may require no treatment. Patients with a normal immune system with or without chronic obstructive pulmonary disease who have three positive cultures for MAC and a small chronic infiltrate will usually respond to a three-drug program such as (a) ethambutol; (b) a macrolide such as clarithromycin or azithromycin; and (c) a rifamycin such as rifampin or rifabutin. Only those patients who have extensive pulmonary disease, are quite ill systemically, or have progressive disease on simpler programs should be given four to seven-drug programs, which may include (a) a quinolone such as ciprofloxacin or ofloxacim; (b) an injectable aminoglycoside such as amikacin or streptomycin; and/or (c) a rifampin derivative such as rifabutin. Unfortunately, such regimens have a high incidence of drug side effects and are difficult to administer outside of specialized centers.

After the patient is culture negative for 1 year, the regimen can be reduced to three to four drugs for an additional year; some recommend continuing with one to two drugs for a third year. When anatomically feasible, early surgical intervention (under chemotherapeutic coverage) is indicated. Bacteriologic conversion rates varying from 40% to 90% have been achieved with such combined medical and surgical therapy. Relapse, however, is common.

Patients with AIDS and MAC infection typically suffer a systemic MAC infection. The manifestations in the lungs of these patients are more components of the systemic infection than of a primary pulmonary process. The aforementioned drugs can be used in these cases; however, their efficacy in AIDS cases is difficult to demonstrate with certainty. Many studies have demonstrated a decrease in colony counts in the blood or sometimes stool or other sites. However, it has been difficult to demonstrate an increase in survival when these medications are used, and some argue that the toxicity of these drugs in patients with AIDS makes therapy counterproductive.

Strict guidelines regarding the less common pathogens are not possible because of the relative lack of available information. M. fortuitum is resistant to most antituberculous

drugs. Chemotherapeutic regimens similar to those for MAC have yielded only limited success. Amikacin, doxycycline, and sulfonamides may show in vitro sensitivity and can be useful clinically. Surgical resection, if feasible, should be considered. Rare pulmonary infections with M. scrofulaceum behave clinically like MAC and appear exceedingly refractory to drug therapy. Disease from M. xenopi demonstrates a variable response to drugs. Results with M. szulgai disease have been more encouraging. As a general rule, a minimum of three drugs to which the organism is sensitive should be used. Both a nontuberculous mycobacterium and M. tuberculosis are sometimes isolated from the same patient. In such cases, therapy directed at M. tuberculosis usually results in clinical resolution.

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36. COCCIDIOIDOMYCOSIS

Antonino Catanzaro

Coccidioides immitis is a dimorphic fungus that grows in the soil in endemic areas, including the lower Sonoran life zone (southern California, Arizona, Nevada, New Mexico, and Texas), as well as in northern Mexico and parts of South America. It proliferates in the mycelial form during the rainy season and forms arthrospores when the climate becomes hot and dry. Large outbreaks of coccidioidomycosis can follow natural disasters, such as earthquakes, which can vigorously disturb soil, causing the release of coccidioides arthrospores.

The primary coccidioidal infection is asymptomatic in 60% of individuals; the remainder experience variable degrees of fever, chills, malaise, cough, dyspnea, chest pain, arthralgias, pharyngitis, and rash. Skin manifestations are common in primary infection, occurring in approximately 5% of men and 25% of women. A fine erythematous maculopapular exanthem, termed *toxic cutaneous erythema*, is said to be very common

but is an extremely evanescent, early event. San Joaquin Valley fever represents a characteristic symptom complex of primary coccidioidomycosis and classically includes erythema nodosum (with or without erythema multiforme), arthralgias, malaise, and fever. The chest roentgenogram is often abnormal, even in asymptomatic individuals, and infiltrates are observed in 80% of patients requiring hospitalization. The infiltrates vary widely in size, location, character, and duration. Hilar adenopathy occurs in 20% of cases and does not influence the prognosis unless it is persistent and accompanied by rising serologic titers. Pleural effusion is detected roentgenographically in less than 10% of symptomatic individuals; in these patients, the effusions tend to be small (<1 L).

In general, physical findings in primary coccidioidomycosis are nonspecific and consistent with those of any *flulike* syndrome. Signs of pulmonary parenchymal consolidation can be present and often are very localized and transient; pleural rubs are unusual. Dissemination, however, can occur, especially in patients with depressed cell-mediated immune (CMI) responses. Certain individuals appear predisposed to disseminated infections, including (in order of decreasing risk) (a) immunocompromised individuals, most notably those with the acquired immunodeficiency syndrome (AIDS); (b) patients taking immunosuppressive drugs, particularly prednisone; (c) individuals of black, Filipino, or American Indian extraction; and (d) possibly those in the last trimester of pregnancy. Pregnancy has long been considered a risk factor, but its importance is unclear. Age more than 55 years is associated with a greater risk of prolonged symptoms, even after 1 year of treatment.

Coccidioidomycosis is considered persistent when symptoms or signs of pulmonary involvement are present beyond 6 to 8 weeks. Manifestations of persistent pulmonary coccidioidomycosis include (a) acute progressive symptomatic pneumonia; (b) chronic progressive pneumonia; (c) pulmonary nodule or nodules (coccidioidomas); and (d) pulmonary cavities, which can hemorrhage, rupture into the pleural space, or undergo spontaneous closure. Coccidioidomas represent isolated residua of active pulmonary disease, and organisms have been cultured from lesions that remained unchanged for decades. Coccidioides cavities may be thin walled and often represent the initial roentgenographic manifestation of infection. The thin-walled cavities have a tendency to expand, presumably because of a check-valve mechanism at their bronchial communication. Most coccidioidal cavities are clinically silent, but hemorrhage, rupture leading to bronchopleural fistulas, and secondary bacterial infection can occur. Empyema can result from either bacterial or fungal causes. In persistent pulmonary coccidioidomycosis, serologic evidence of activity (e.g., elevated complement fixation [CF] titers is frequently absent, but when present, should raise the possibility of intrapulmonary dissemination).

A few individuals develop progressive pulmonary disease or disseminated infection. Certain signs also imply a worse prognosis and an increased risk of dissemination. The signs include (a) elevated CF titers; (b) pulmonary infiltrates or hilar or paratracheal adenopathy that persists more than 6 weeks; and (c) significant weight loss. Disseminated coccidioidomycosis occurs infrequently, usually in individuals with impaired CMI. CMI can be depressed by an obvious cause such as systemic illness (e.g., AIDS, Hodgkin's disease) or certain pharmacologic agents (e.g., steroids or cytotoxic agents), but usually such depression is of obscure cause. Typical miliary lesions occur in 4% of cases. The most frequent sites of dissemination are the skin, bones, soft tissues, and meninges; however, single or multiple mass lesions or abscesses can occur in any organ. Cutaneous fistula formation from deep-seated lesions is common. Patients with facial lesions caused by coccidioidomycosis have a greater chance of developing meningitis than patients who have lesions on the body only. This association may allow for earlier detection and treatment of coccidioidomycosis meningitis. Meningitis is the most ominous form of dissemination because of the anatomic disruption that ensues and because of the difficulty in getting drugs to the site of infection. If dissemination has occurred or is suspected, a careful evaluation of its extent should be undertaken, including analysis of the cerebrospinal fluid for CF titer. However, cerebrospinal fluid can be negative in 25% of cases on initial examination; a spinal tap should be repeated in 1 or 2 weeks if clinical suspicion is high. Bone scans are very useful in the search for subclinical sites of dissemination.

Coccidioidomycosis is usually diagnosed by appropriate interpretation of the skin test and serology. The precipitin tests become positive early in the course of infection (1–3 weeks), whereas CF and immunodiffusion tests are more delayed in their

conversion to positive. The latex agglutination test is problematic. It detects both immunoglobulin G and M (IgG, IgM) antibodies; unfortunately, it is positive in up to 10% of normals and negative in 30% of confirmed cases of coccidioidomycosis. For these reasons, it is usually necessary to confirm the results of latex agglutination. The CF and immunodiffusion tests are important because titers tend to correlate with the extent of infection and are useful with respect to prognosis and management. CF titers are greater than 1:32 or 1:64 in 90% of disseminated disease; however, a high titer is not always present in disseminated disease. Although they are relatively sensitive, high CF titers by themselves are not sufficient evidence to diagnose dissemination. The coccidioidal CF test can cross-react to antibodies induced by other fungal infections, most notably in patients with histoplasmosis. CF tests employing spherulin antigen are even more nonspecific. The immunodiffusion test is ideally suited to demonstrate antigenic cross-reactivity. A new enzyme-linked immunosorbent assay for coccidioidal antigens allows coccidioidomycosis to be detected early. It is sometimes difficult to correlate the results of this test with benchmarks established for complement fixation antibody levels. Skin tests using either the standard coccidioidin antigen or the spherulin antigen become positive by the second or third week in nearly all individuals with acute self-limited infection. Neither antigen (coccidioidin or spherulin) offers consistent advantage over the other in clinical testing. Unfortunately, a number of problems have occurred with the manufacture of these antigens, resulting in sporadic availability.

Treatment options should be considered only after evaluating clinical characteristics such as (a) the extent of disease, particularly involvement of the central nervous systems or bones; (b) the immune response of the host to the infection in terms of delayed-type hypersensitivity and antibody response; and (c) demographic risk factors such as age, gender, and ethnicity. Treatment guidelines are being developed based on these individual patient characteristics.

Amphotericin B was the first antifungal demonstrated to be efficacious in the treatment of coccidioidomycosis. For many years, it was the only agent active against *C. immitis*. Therefore, amphotericin B has been regarded as the drug of choice in the treatment of coccidioidomycosis. Unfortunately, amphotericin B is not absorbed orally; it distributes poorly to the tissues and is highly toxic. Recently, orally absorbed azoles have been demonstrated to yield good therapeutic results in many situations. Ketoconazole has been approved for use in coccidioidomycosis. However, to be active against *C. immitis*, ketoconazole must be used at a dosage of 200 to 400 mg/d, which can cause gastrointestinal irritation, hepatitis, and adrenal and testicular dysfunction. The triazoles, fluconazole and itraconazole, are more active and less toxic than ketoconazole and have been demonstrated to be efficacious in open trials. Either one should be started at 400 mg/d. Fluconazole can be given intravenously (if necessary) or at higher doses, as needed. Itraconazole is not available in a parenteral formulation and has unacceptable toxicities at dosages over 600 mg/d.

Neither fluconazole nor itraconazole are approved by the US Food and Drug Administration for coccidioidomycosis; however, they are both widely used to treat patients with non–life-threatening coccidioidomycosis. In fact, I and many experts share the opinion that triazoles are the first-line drugs of choice for treating coccidioidomycosis. Along this line of reasoning, amphotericin would be considered a *niche drug*: useful only in special situations such as pregnancy, critical illness, and failed therapy with azoles. Both fluconazole and itraconazole are very effective for the treatment of most forms of coccidioidomycosis. Itraconazole is more toxic, particularly at higher doses, and can interact with other drugs. Fluconazole is less toxic and can be given at much higher doses in those cases that do not respond to conventional doses. In refractory cases, patients have tolerated as much as 2 g/d without toxicity. In these cases, when control of the disease is established, the dose can be lowered. Fluconazole (200 or 400 mg/d) is well tolerated and fairly effective for the treatment of chronic coccidioidomycosis. However, alopecia is a side effect associated with higher doses (400 mg/d) or fluconazole given for 2 months or longer. Reversal of alopecia may be achieved by discontinuing therapy or reducing the daily dose.

Coccidioidal meningitis is usually treated with fluconazole. Although the best study reported the results of treatment with 400 mg/d, most clinicians start at 800 mg/d for this indication. Amphotericin B does not cross the blood–brain barrier in concentrations

needed to treat coccidioidal meningitis. Therefore, it must be administered intrathecally to treat meningitis. Lumbar injections are easiest but almost always result in chemical arachnoiditis, although arachnoiditis has also been reported on fluconazole. Cisternal injections require a skilled practitioner but give better results. An intraventricular catheter with an Ommaya reservoir circumvents some problems; however, if obstruction of the outflow of fluid from the ventricles exists, the drug may not get to the site of the infection. Fluconazole and itraconazole can be used to treat meningitis. However, when the drug is stopped, meningitis is likely to recur. For this reason, therapy should continue for life.

Alternate treatments include amphotericin B lipid complex and ketoconazole. Amphotericin B lipid complex has been shown to be a successful treatment, especially when patients experience toxicity from other treatments. Ketoconazole is a second-line drug for coccidioidomycosis. The relapse rate is high when this drug is discontinued and it should not be used for patients who are seriously ill with coccidioidomycosis or who have coccidioidomycosis meningitis. Negative skin tests and a titer of $\geq 1:256$ are associated with an increased risk of coccidioidomycosis relapse.

In general, coccidioidomycosis does not require surgical intervention. However, surgery is critical in several situations, specifically in establishing the diagnosis in difficult cases, for draining pus, in treating certain problems such as life-threatening hemoptysis, or as an adjunct to medical treatment of tenosynovitis.

Control and prevention of coccidioidomycosis can be improved by early diagnosis, administering specific tests (including obtaining a travel history) and proper case management including a multidisciplinary approach. In addition, research efforts should be expanded and institutional policies should be reevaluated. The Valley Fever Vaccine Project has funded several investigators to create vaccines and several candidate molecules are being developed.

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37. HISTOPLASMOSIS

Timothy A. Morris and Hyong S. Kim

The term *histoplasmosis* refers to any one of a variety of disorders resulting from infection with the dimorphic fungus *Histoplasma capsulatum*. Although histoplasmosis is usually self-limiting and causes few or no symptoms, massive inhalation can cause acute respiratory disease. In addition, a variety of serious pathologic conditions can result if the immune response to *H. capsulatum* is either ineffective or inappropriately severe.

Histoplasma capsulatum has a world-wide distribution but is particularly endemic to the great river valleys of the midwestern to southern United States. *H. capsulatum* lives as a mycelium in nitrogen-rich soil near large amounts of bird droppings, such as are found in starling roosts or chicken houses. Bats may carry the fungus enterically, making bat guano particularly infested with *H. capsulatum*.

Infection with *H. capsulatum* by inhalation is ubiquitous in endemic areas. Because symptoms are generally mild and nonspecific, acute histoplasmosis is usually recognized only after a large exposure (e.g., razing of an abandoned chicken house) causes an epidemic of new cases.

Only the mycelia generate spores (microconidia), which are small enough to be aerosolized and, if inhaled, to reach the alveoli. At the host's body temperature, the microconidia grow into the yeast form. After an ineffective neutrophil response, alveolar macrophages phagocytize the yeast. They are not destroyed, but travel within the

macrophages to regional lymph nodes, and then disseminate hematogenously. Within 2 weeks, T lymphocytes develop a specific cell-mediated immunity and *arm* macrophages to eradicate the fungus throughout the body. Where yeast collection is too large, they are not killed but are contained within a fibrotic granuloma, which eventually calcifies. The high frequency of pulmonary and splenic calcifications in residents of endemic areas is evidence of the ubiquitous nature of this infection.

In the normal host, histoplasmosis is usually asymptomatic. Some patients suffer an influenzalike syndrome 1 to 2 weeks after infection, which in women can be accompanied by erythema nodosum. Others may develop acute pulmonary histoplasmosis, a self-limited pneumonia characterized by consolidation and hilar lymph node enlargement. Recovery is generally within 2 weeks. Illnesses lasting longer than this may portend progressive dissemination, and some would recommend that antifungal medication be used in this instance. It can take months for the chest film demonstrates show clearance, and residual small scars will calcify over several years.

A massive inhalation inoculum can occur if fungal deposits are stirred up and inhaled in an enclosed space (such as can happen if a spelunker disturbs a large bat lair). The enormous inflammatory reaction can cause acute respiratory insufficiency about 2 weeks after exposure. Chest radiograph demonstrates scattered infiltrates and hilar adenopathy. Corticosteroids may be necessary, as well as a brief course of amphotericin B to decrease the fungal load.

Should the cell-mediated immune response be insufficient, progressive dissemination occurs inside macrophages. Progressive disseminated histoplasmosis can cause an interstitial pneumonitis and also commonly involves the spleen, liver, bone marrow, lymph nodes, gastrointestinal tract, adrenal glands, meningeal vessels, and heart valves, particularly the aortic valves. Depending on the degree of immune insufficiency, the course can run from severe sepsis to chronic consumption. An acute form occurs in infants and severely immunosuppressed adults, which can lead to death within weeks if untreated. In other cases, a deteriorating course can run for several months or even years. Smears and cultures of the involved sites usually provide the diagnosis. Recommended treatment for severe or moderately severe cases is with amphotericin B (50 mg/d titrated to clinical response or to a total dose of 35 mg/kg over 2–4 months) followed by maintenance therapy for a minimum of 6 months. In patients with mild or subacute cases of progressive dissemination, an effective induction can be achieved alternatively with itraconazole (400 mg/d) or, for immunocompetent patients, with ketoconazole (400–800 mg/d). For severe, acquired immune deficiency syndrome (AIDS)-related progressive, disseminated histoplasmosis, the recommended total amphotericin B dose is at least 15 mg/kg followed by lifelong suppression therapy with itraconazole (200 mg/d). Recent prospective trials suggest itraconazole is superior to ketoconazole and fluconazole in both the induction (nonsevere cases) and maintenance phases of therapy.

Histoplasma capsulatum can also colonize the distorted architecture of an emphysematous lung, causing chronic pulmonary histoplasmosis. Infected cavities can enlarge and worsen gas exchange in the already compromised lungs. In addition, periodic spillage of the fungi can cause recurrent pneumonia and eventual fibrosis in dependent lung parenchyma. Although the appearance can simulate cavitary tuberculosis, the sputum culture will grow *H. capsulatum* in one third to one half of cases. Itraconazole (200 mg twice daily) or ketoconazole (400 mg/d) is usually effective, but amphotericin B may be necessary for severe cases. Because of a high relapse rate among patients with chronic pulmonary histoplasmosis, some authors recommend at least 12 months of therapy. If the patient's lung function will allow surgery, resection of the infected cavity is generally curative.

Should the granulomatous response to *H. capsulatum* antigen be vigorous in the lung parenchyma, 1- to 2-cm nodules called *histoplasmomas* can form. The histoplasmoma can enlarge at a rate of 2 mm/y but poses no danger and does not require treatment. It can be mistaken for a lung cancer, however, and prompt unnecessary resection. The presence of a small central calcification with concentric calcified laminations may identify this lesion on chest radiograph.

In the mediastinum, enlarging caseous lymph nodes can mat together to form a large mass inside a common capsule. The resulting mediastinal granuloma is most commonly found in the right peritracheal area; it can enlarge up to 10 cm, causing

extrinsic compression of nearby structures (e.g., the esophagus). Symptomatic mediastinal granuloma can be cured by surgical resection, although some authors recommend a trial of oral antifungal agents first.

Sclerosing mediastinitis is the most extreme example of immunologic overreaction, in which a small amount of *H. capsulatum* antigen stimulates severe fibrosis. The reaction is so intense that fibroblasts from inside adjacent vital structures are recruited and fuse the mediastinal contents into a rock-hard mass. Constriction of the esophagus, pulmonary arteries, pulmonary veins, pericardium, and even the bronchi may ensue. Corticosteroids are of equivocal benefit. Reports of live organisms in surgical specimens from these patients prompt some optimistic clinicians to treat fibrosing mediastinitis with antifungal agents. Although surgical resection is not possible, heroic surgical procedures have been performed to bypass obstructed blood vessels.

The diagnosis of histoplasmosis is best made by culture of the affected sites. Because the yield of culture is variable among different manifestations of the disease, other tests may be useful. The fungi can be seen within macrophages on Wright's or silver stain, but care must be taken to distinguish them from other intracellular pathogens. Skin testing becomes positive only 3 weeks after acute exposure and is too common in endemic areas to be of much use in active disease. Another consideration is that skin testing can cause false-positive results on serologic tests.

Antibodies to histoplasmin appear in the serum 2 to 3 weeks after exposure and can be detected by complement fixation in 85% of cases. Because of the prevalence of positive reactions in endemic areas, presumptive evidence of infection requires a dilution titer of greater than 1:32 or an acute fourfold rise in titer. Unfortunately, titers this high are seen in only about half of active infections. Immunodiffusion or counterimmunoelectrophoresis detects antibodies against two *Histoplasma* antigens, *m* and *h*. Antibodies to m are found in most histoplasmosis patients but can also be induced by remote asymptomatic exposure or even skin testing. Finding both m and h antibodies is specific for histoplasmosis but much less sensitive than other serologic tests.

The T-cell deficit in patients with AIDS makes them particularly vulnerable to infection from *Histoplasma* organisms. Progressive disseminated histoplasmosis has been found in up to 5% of patients with AIDS living in endemic areas and even in a few who had relocated from endemic areas years ago. Progressive dissemination can occur either from reactivation of latent infection or from new exposure. Although fever is present in nearly all patients, respiratory complaints and chest radiograph changes are found in only half. Of patients with AIDS, 12% with histoplasmosis present with a sepsis syndrome. The enormous fungal load frequently results in positive smears and cultures of blood, respiratory secretions, urine, and bone marrow. However, up to 15% of these patients can have negative smears and cultures despite multiple sampling. Furthermore, standard antibody testing in this population is more frequently negative. A more-reliable test in this population is the detection *H. capsulatum* polysaccharide antigen (HPA) in body fluids. In AIDS patients with progressive disseminated histoplasmosis, HPA can be rapidly detected in urine (97% of cases), blood (83%), and cerebrospinal fluid (66%). HPA levels can also be used to guide therapy and detect relapse.

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38. BLASTOMYCOSIS

David W. Dockweiler

Blastomycosis is a relatively uncommon disease caused by the dimorphic fungus *Blastomyces dermatitidis*. Following introduction by the respiratory route into the host, the organism can give rise to a spectrum of clinical syndromes ranging from an acute, self-limited, flulike illness to rapidly progressive, widely disseminated, fatal disease.

Blastomyces dermatitidis grows in mycelial form when cultured at 25°C and as a single budding yeast with a doubly refractive cell wall within human tissues at 37°C. The primary reservoir of *B. dermatitidis* appears to be soil, as was demonstrated by the isolation of the organism from the soil in association with an epidemic in 1984.

Because the vast majority of cases have been described on the North American continent in an endemic area that includes the southeastern and central United States, as well as the region around the Great Lakes, the disease has also been known as North American blastomycosis. With the demonstration of cases in Europe, Africa, South America, and the Middle East, this term is clearly no longer appropriate.

Blastomycosis is considered to be a disease of middle-aged men, although cases have been described in both sexes, with ages ranging from newborn to the elderly. A significant number of patients have a history of outdoor exposure, especially hunting. Interestingly, canine blastomycosis, a condition similar to human disease, is more commonly seen in animals that are used in hunting, suggesting exposure to both humans and animals from a common outdoor source. Although blastomycosis is not an opportunistic infection *per se*, the disease has been described in a number of immunosuppressed patients, such as those with renal transplants. Not surprisingly, a number of patients with the acquired immunodeficiency syndrome (AIDS) have been found to have blastomycosis, often with severe, disseminated disease and a high incidence (40%) of central nervous system involvement.

Primary infection with *B. dermatitidis* almost always results from inhalation of fungal spores emanating from the soil or other source; person-to-person transmission by aerosol has never been documented. Communicability among humans can take place through sexual contact (via prostatic secretions) or from maternal-fetal transmission, but these occurrences are unusual. A laboratory accident has resulted in disease from percutaneous inoculation.

Following deposition of the inhaled spores in the alveoli, an inflammatory response is initiated that consists of polymorphonuclear leukocytes, macrophages, and epithelioid cells. Granuloma formation follows in most cases. From this beginning, depending on factors such as host resistance, the dose inhaled, and other unknowns, several clinical courses are possible: (a) mild or clinically silent pulmonary involvement that

spontaneously resolves; (b) acute pneumonitis with nonspecific symptoms such as fever, cough, purulent sputum, chills, myalgias, pleuritic chest pain, and, occasionally, erythema nodosum; (c) severe progressive pulmonary involvement leading to hypoxemia, respiratory failure, and prostration; (d) the development of chronic pulmonary infection, resembling other fungal diseases or tuberculosis, and presenting with constitutional complaints such as malaise, weight loss, chronic cough, fever, and blood-tinged sputum (but rarely significant hemoptysis); and (e) disseminated disease, which can complicate any pattern of pulmonary involvement or can occur *in isolation*, representing reactivation of the disease long after the primary focus of infection has resolved. Dissemination is said to take place in up to 70% of patients with chronic disease, and multiple organ involvement is the rule.

Although disseminated blastomycosis can manifest anywhere, the skin, as the organism's name suggests, is by far the most commonly involved organ. The skin lesions typically begin as small subcutaneous nodules or pustules that can grow rapidly and ulcerate to form large verrucose ulcers with heaped-up edges. Although skin lesions can occur at any site, the face and trunk are favored. Bony lesions, typically osteolytic, are next in frequency. Areas commonly involved include the bones of the extremities, vertebral bodies, skull, ribs, and pelvis. Overlying soft tissue can be involved, joint spaces may be infected by direct extension, and vertebral body disease can give rise to paraspinous abscesses. The male genital tract (epididymis, testes, prostate) has been estimated to be involved in approximately 10% of patients with disseminated disease. Infected prostatic secretions have been documented and presumably explain sexual transmission of the disease. Less often, laryngeal involvement is seen, which can be difficult to distinguish grossly from carcinoma. Adrenal involvement is not uncommon but rarely results in adrenal insufficiency. Meningeal blastomycosis is rare in immunocompetent hosts but occurs more frequently in patients with AIDS.

Roentgenographic findings are variable, and correlate only moderately well with the clinical presentation. In patients with acute pneumonia, the chest x-ray and computed tomography (CT) appearances are nonspecific and include consolidative, nodular, or interstitial infiltrates that can be segmental or nonsegmental. Multiple lobes may be involved, although upper lobe involvement appears to be more common. Despite the relatively common occurrence of pleurisy, pleural effusions are unusual. Cavitary changes have been reported in up to 10% of cases. Chronic forms of blastomycosis can present as central parenchymal masses, resembling bronchogenic carcinoma. Hilar and mediastinal adenopathy appear to be infrequent, even on CT examination. Lymph node calcification, common in histoplasmosis, is rare in blastomycosis.

Standard laboratory studies are nonspecific. Hematologic abnormalities (e.g., anemia, leukocytosis) are variable and rarely marked. Serum chemistries are usually normal. Skin tests for blastomycosis have proved to be useless because of low specificity and sensitivity. Serologic tests are available, but poor sensitivity and specificity also limit their usefulness, particularly in areas where other deep mycoses (e.g., histoplasmosis or coccidioidomycosis) are endemic. Additionally, immunocompromised patients, such as those with AIDS, frequently have negative serologies despite widely disseminated disease. The serologic tests commonly used include (a) an enzyme immunoassay (EIA) for *Blastomyces* antigen A, which is reasonably sensitive (<80%), although specificity is limited; and (b) an immunodiffusion (ID) technique using the same antigen, which is highly specific, but insensitive. These tests are best used in conjunction, by screening with the sensitive EIA and confirming the disease serologically with the specific ID. A newer EIA based on the principle of antigen-capture has been said to be specific for blastomycosis without sacrificing sensitivity, but awaits confirmatory studies.

Definitive diagnosis of the disease requires the demonstration of the fungus in the tissues, either microscopically or by culture. *B. dermatitidis* is often found in sputum smears (prepared using potassium hydroxide or Papanicolaou's stain), bronchoscopy washings, pleural fluid, urine (especially following prostate massage), or tissue biopsy specimens. The organism is best demonstrated with methenamine silver or para-aminosalicylic acid stains. Culture of the organism is possible from all of the above sites, but growth requires 1 to 3 weeks, a delay that presents a problem in the acutely ill patient. Once cultured, exoantigen testing with a DNA probe will rapidly and reliably identify *B. dermatitidis*.

The decision to treat patients with blastomycosis is based on clinical assessment. Because mild, acute, pulmonary forms of the disease are usually self-limited, treatment is probably not required in immunocompetent patients. They can be observed closely for progression of disease, which would necessitate treatment. Patients having more severe pulmonary involvement, toxemia, hypoxemia, progressive chronic disease, disseminated disease, and those who are immunosuppressed should receive drug therapy.

Itraconazole, an oral antifungal triazole, is believed to be the drug of choice in the treatment of nonmeningeal, non–life-threatening forms of blastomycosis. Early studies have found response rates of more than 90%, results as good or better than with ketoconazole, but with significantly less toxicity. Furthermore, itraconazole has been shown to be effective in treating ketoconazole treatment failures. As with the other oral azoles, itraconazole is fungistatic and does not cross the blood–brain barrier; therefore, its use should be limited to treating immunocompetent individuals with nonmeningeal, non–life-threatening disease. A dosage of 200 mg/d for 6 months is recommended, unless disease progresses, in which case the dosage should be increased to 400 mg/d. Itraconazole is also recommended as maintenance therapy for patients with AIDS and disseminated blastomycosis who have already had an initial course of amphotericin B.

Ketoconazole is also effective in cases of both disseminated and pulmonary disease, although treatment failures and relapses have been noted. To minimize adverse effects, 400 mg/d is recommended as the starting dose, with higher doses (up to 800 mg/d) reserved for patients whose disease progresses or who develop a new focus of infection while on therapy. Treatment should continue for a minimum of 6 months or until radiographic stability or resolution occurs.

A third oral antifungal, fluconazole, does not appear to be as effective as itraconazole, based on the need for higher drug doses to achieve nearly comparable results. The higher incidence of (mostly minor) side effects and the higher cost of fluconazole make it a second- or third-line choice for treatment of blastomycosis.

Amphotericin B remains the drug of choice for blastomycosis during severe life-threatening infections, meningeal disease, and infections in patients with AIDS and after failure of oral antifungal medications. The clinical response to amphotericin B is usually excellent, although side effects can be problematic. When given in a total dose of 2 g over a period of 10 to 12 weeks, the incidence of relapse is well below 10%.

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39. *ASPERGILLUS* LUNG DISEASE

Stephen W. Crawford

Aspergillus species (AS) rarely cause disease in normal individuals but can be a significant problem in susceptible patients. The species *A. fumigatus*, *A. flavus*, and *A. niger* can all cause infection, but *A. fumigatus* is responsible for more than 90% of human *Aspergillus* infection. AS are ubiquitous worldwide and often contaminate laboratory specimens exposed to unfiltered air. The fungi are dimorphic, existing as spores and as mycelia. Outside the host, the fungi produce thick-walled spores, resistant to desiccation,

which subsequently may be inhaled from ambient air; person-to-person transmission has not been reported. Following inhalation of spores, a transient saprophytic infection may result; however, individuals with underlying lung disease can develop persistent colonization. In the saprophytic form, the organism assumes a complex pattern of mycelial growth, forming characteristic fruiting bodies (conidiophores) that contain 3 μm diameter spores (conidia). During tissue invasion, the organism produces filamentous septate hyphae having characteristic 45-degree branch points.

Depending on the particular susceptibility of the host, aspergilla can cause one of three distinct pulmonary syndromes: (a) aspergilloma, (b) allergic bronchopulmonary aspergillosis, and (c) invasive aspergillosis. An aspergilloma (mycetoma or *fungus ball*) is a mass of mycelial elements, fibrin, mucus, and cellular debris situated within a preexistent pulmonary cavity or ectatic bronchus—often the residual damage from previous tuberculosis, sarcoidosis, coccidioidomycosis, histoplasmosis, or pneumoconiosis. The fungus behaves as a saprophyte and does not invade the cavity wall. Aspergillomas are not uncommon; in a prospective study of more than 500 tuberculosis patients with culture-negative open cavities, its incidence was in excess of 15%.

An aspergilloma can present merely as an asymptomatic abnormality on chest roentgenogram or with significant hemoptysis. Hemoptysis occurs in 45% to 85% of cases and is generally minimal and recurrent, although occasionally it can be massive and life threatening. Rarely, constitutional symptoms (e.g., fever, malaise, weight loss) occur, possibly reflecting stimulation of immune mechanisms or secondary infection with bacteria. Physical examination is nonspecific, frequently dominated by findings of the underlying lung disease. The chest roentgenogram characteristically reveals a cavity containing a shadow separated superiorly from the cavity walls by a crescentic layer of air. Such findings are usually located in the upper lobes, reflecting the frequency of disease within old tuberculous cavities. Overlying pleural thickening is common. Fluoroscopy may demonstrate mobility of the shadow within the cavity after positional changes. Routine laboratory examination usually is not helpful. Eosinophilia is uncommon. Serum precipitins are present in 93% to 100% of cases and their absence makes a diagnosis of aspergilloma unlikely. Immediate dermal hypersensitivity to a skin test is unusual. Pulmonary function studies reflect only the underlying disease.

The differential diagnosis of aspergilloma includes mycetoma secondary to other fungi, disintegrating echinococcal cysts, intracavitary blood clot, necrotic tissue within a cavitating carcinoma, or lung abscess. The diagnosis is usually based on a typical chest roentgenogram, the recovery of *Aspergillus* organisms from multiple sputum or surgical material, and the presence of serum precipitins.

The treatment of aspergilloma is controversial. When associated with frequent or life-threatening hemoptysis, surgical resection is the treatment of choice. Although some advocate prophylactic surgery for nearly all aspergillomata, the approach should be individualized. In many patients, the process will have a benign course, and the risk of surgery is high because of underlying lung disease. Treatment with intracavitary or systemic antifungal agents has a record of variable success. An aspergilloma may spontaneously disappear in as many as 10% of cases, often coincident with the resolution of concomitant bacterial pulmonary infection. This characteristic makes evaluation of medical regimens difficult. Constitutional symptoms, when present, often respond to steroids.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease to *Aspergillus* antigens. The peak incidence is in the fourth to fifth decades. Patients with long-standing atopic asthma are usually affected. An increased incidence of ABPA has been reported in England during winter months when air contains the greatest quantity of *Aspergillus* spores.

The pathologic changes of ABPA are characterized by ectasia of central airways, often accompanied by mucoid impaction. Distal airways are usually spared. Histologically, round cells and eosinophils infiltrate bronchial walls, and granuloma form in some cases. Blood vessels are spared or only secondarily involved. Hyphae of *Aspergillus* organisms can be discerned adjacent to the bronchial wall, but invasion does not occur.

Clinically, ABPA presents with bronchospasm that initially may be episodic. Later in its course, the symptoms tend to become more chronic. The clinical course is characterized by cough productive of mucous plugs, hemoptysis, intermittent febrile episodes, chest pain, and, often, recurrent pneumonias. Physical examination is nonspecific,

revealing wheezes and rhonchi. Serial chest roentgenograms may show fleeting infiltrates occurring more commonly in the upper lung fields. The typical branching homogeneous (*gloved finger*) shadows of mucoid impaction are often seen, as are the *tramline* and *ring* shadows of thickened bronchial walls. Upper lobe fibrosis progressing to honeycombing can occur in long-standing disease. Bronchography or computed tomography scans often identify pathognomonic central bronchiectasis that characteristically terminates abruptly, leaving distal airways relatively normal. Both peripheral and sputum eosinophilia are generally present. Expectorated mucous plugs are characteristically brownish and, when appropriately stained, reveal abundant eosinophils and mycelial elements. Sputum culture commonly reveals the fungus (60% to 100%). Total immunoglobulin E (IgE) levels are nearly always elevated, and constitute a useful screening test. Specific precipitating antibodies are present in 50% to 90% of patients. Immediate (type I) and late (type III) dermal hypersensitivity to *Aspergillus* antigen is nearly universal (87% to 100%). Pulmonary function studies show airways obstruction; however, a restrictive component with decreased diffusing capacity for carbon monoxide can also be present in long-standing disease.

The differential diagnosis of ABPA includes asthma, pulmonary infiltration with eosinophilia syndromes, helminthic lung disease, and other types of hypersensitivity pneumonitis. Recovery of *Aspergillus* organisms from sputum culture in the proper setting should prompt a high index of suspicion, but overinterpretation is dangerous because of the high incidence of laboratory contamination. Four major findings suggest the diagnosis of ABPA: (a) recurrent infiltrates on chest roentgenograms, (b) blood or sputum eosinophilia, (c) asthma, and (d) immediate and late (6–8 hours) dermal hypersensitivity to *Aspergillus* antigens. The presence of serum precipitins further substantiates the diagnosis. Bronchial challenge with specific antigen is positive. In the absence of these criteria, the diagnosis of ABPA is doubtful.

The management of ABPA often requires steroids, bronchodilators, and cromolyn sodium. Systemic steroid therapy completely controls the clinical manifestations. Within a few days of initiating relatively high doses of steroids, symptoms clear, roentgenographic abnormalities resolve, and serum IgE levels fall. A fall in precipitin levels also occurs but is somewhat delayed. The optimal duration of steroid therapy is not well defined. Steroids should be continued until the chest roentgenogram is clear. In some patients, inhaled corticosteroids—in high doses—have allowed discontinuation of oral steroids. Hyposensitization therapy has been disappointing, and avoidance of this ubiquitous saprophyte is impossible. Treatment with itraconazole has been shown to improve lung function and reduce steroid requirements among patients requiring prolonged treatment for persistent ABPA.

Control of the inflammatory process is important. Evidence indicates that long-standing or repeated episodes of pulmonary infiltration lead to bronchiectasis and fibrosis. Among patients with mild bronchospasm, steroid dosage can be reduced and symptoms may be controlled with bronchodilators or inhaled steroids after roentgenographic clearing. A disparity may exist between the clinical manifestations and the roentgenographic (and presumably histologic) changes, and vigilance must be maintained for exacerbation of the disease. An increase in the level of serum IgE or roentgenographic worsening can signal the need for resumption of systemic steroid therapy. With adequate management, the prognosis for ABPA is good and long remissions are often achieved.

Invasive aspergillosis occurs almost solely in immunocompromised patients. The major risks to infection are prolonged neutropenia and high-dose corticosteroids. The disease is generally felt to evolve from endogenous (saprophytic) infection. High *Aspergillus* spore counts, however, have been found in ambient air or near ventilation ducts of hospitals in which clusters of invasive aspergillosis have occurred. This suggests that exogenous acquisition occurs and, more importantly, some cases might be prevented by an appropriate monitoring or filtration of ambient air.

Invasive aspergillosis involves the lungs in more than 90% of cases, usually manifesting as a focal or multifocal, necrotizing bronchopneumonia. Pathologic studies reveal that invading *Aspergillus* hyphae grow into the pulmonary vessels, often resulting in infarction of lung tissue and hemorrhagic pneumonia. Aggressive spread is the hallmark of this disease; if patients survive long enough, endocarditis can develop, with subsequent metastatic spread of the infection.

The clinical manifestations can include dyspnea, tachypnea, nonproductive cough, pleuritic chest pain, and fever. They can appear abruptly or develop insidiously, mimicking the bacterial or viral infections that are common in the susceptible patient population. Physical findings are nonspecific. Chest roentgenograms show bronchopneumonia or an interstitial process, often with areas of cavitation. Ventilation and perfusion scans may suggest vascular disease. Serum precipitins are usually absent. Culture of the sputum is generally unrewarding. The finding of hyphae in the bronchoalveolar lavage fluid in immunocompromised hosts that are suspected of having invasive pulmonary aspergillosis is a specific but not sensitive indicator of invasive aspergillosis. Transbronchial biopsy by fiberoptic bronchoscope or open lung biopsy is rarely indicated because of the low yield. Identifying the fungus in lung tissue or recovery of the organism from blood confirms the diagnosis, but is seldom possible and is not required to initiate treatment. Because of the aggressive nature of the infection, empiric treatment is often necessary before laboratory confirmation—especially in severely immunocompromised hosts such as bone marrow transplant recipients.

The differential diagnosis includes pneumonia caused by any of the many organisms infecting the immunocompromised host (e.g., other fungi, *Nocardia*, viruses, *Pneumocystis*, bacteria), as well as pulmonary involvement by an underlying neoplasm or pneumonitis secondary to the toxic effects of radiation or chemotherapy. Clinically, invasive aspergillosis is difficult to distinguish from these other disease processes without tissue examination or cultural confirmation from the blood or closed-tissue spaces.

Therapy for invasive aspergillosis should, if possible, include measures to modify the underlying immunocompromised state of the host. Treatment with amphotericin B should be initiated, but the results are often disappointing in severely compromised hosts; fatal outcomes are all too common. The compromised condition of the patient, coupled with difficulty or delay in making the diagnosis, accounts for the high mortality rate of this infection. Those series reporting improved survival in cancer patients with invasive aspergillosis stress two important elements of care: (a) early modifications in the immunosuppressive regimen; and (b) early institution of intravenous amphotericin B. Trials combining amphotericin B with flucytosine in the treatment of invasive aspergillosis have shown only questionable evidence of additive effects. Itraconazole has shown some promise in clinical trials but is available only in the oral form. Amphotericin B can be incorporated into lipophilic liposomal vesicles or complexed with lipid compounds. Three currently marketed lipid formulations of amphotericin B are available: Abelcet (ABLC, or amphotericin B lipid complex); Amphotec (ABCD, or amphotericin B colloidal dispersion; Amphocil); and AmBisome (liposomal amphotericin). The main advantage of lipid formulations of amphotericin B is the ability to administer larger doses of amphotericin B with minimal renal and central nervous system toxicity. Liposomal amphotericin B may be the most appropriate agent for treating proved or suspected invasive aspergillosis in patients at risk for severe adverse effects.

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40. NOCARDIOSIS

Antonino Catanzaro

Nocardia infections occur mostly in men (90%), with 500 to 1000 cases recognized each year in the United States. *Nocardia* is a soil saprophyte, and infection is thought to result from inhalation of airborne mycelial fragments or spores or by direct inoculation. Human-to-human transmission has not been reported. *Nocardia asteroides* is usually responsible for visceral infections, and *N. brasiliensis* is usually responsible for direct inoculations to the skin and lymphangitic spread.

Nocardia is a gram-positive, partially acid-fast, and aerobic organism that causes suppurative and granulomatous lesions in humans. The organisms formerly were classified as fungi because of their profuse mycelial development with true branching. *Nocardia* was reclassified as bacteria (*Mycobacteriaceae*), however, because of the lack of chitin or cellulose within its cell wall and other biochemical properties.

Pathologically, acute *Nocardia* infections produce large numbers of small abscesses, a cellular infiltrate of lymphocytes, giant and foam cells, and extensive fibrosis. *Nocardia* has been reported to form *sulfur granules*.

One or more predisposing factors are usually present when *Nocardia* infections are diagnosed: (a) pulmonary pathology such as chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, and so on; or (2) systemic immunosuppression such as the acquired immunodeficiency syndrome (AIDS), transplantation, malignancy, alcoholism, or diabetes mellitus. In cases wherein no systemic immunosuppression occurs, the infection is usually confined to the lungs. Infection can be acute or chronic. The most common symptoms are cough, purulent sputum (occasionally bloody), chest pain, weight loss, and night sweats.

Nocardia is considered an opportunistic infection in at least half of the cases, with malignancy, immunosuppression, and organ transplantation being the most common underlying problems. In these cases, infection can present similarly to acute bacterial pneumonia.

Acute infection can present as an isolated lung abscess or bronchopneumonia that can subsequently form an abscess. Consolidation and large irregular nodules, often cavitary, occur commonly. However, nodules, masses, and interstitial patterns also occur. Pleural effusions are common. Lymph nodes can be enlarged. Spread to other parts of the lung, pleura, or chest wall rarely occurs. Chronic infection can present as small abscess(es) or chronic fibronodular disease. Such lesions may be confined to a small portion of the lungs or scattered throughout the lungs, mimicking miliary tuberculosis. Sinus tracts and perforation of the chest wall can occur. Airway colonization is possible, and a few well-documented cases have been described in which the organism was repeatedly isolated from the sputum in the absence of disease. *Nocardia* also can invade preexisting pulmonary cavities, forming a *fungus* ball.

Extrapulmonary presentations may include primary cutaneous inoculation with lymphangitic spread or dissemination after a pulmonary or oropharyngeal infection. Spread is usually to the central nervous system, causing meningitis or multiple brain abscesses. Rare cases of widespread dissemination have been reported, usually in individuals with diseases known to interfere with cell-mediated immunity.

Most clinicians feel that the isolation of *Nocardia* organisms from sputum, tissue, or other body fluids represents prima facie evidence for nocardiosis. In identifying *Nocardia* organisms, multiple clinical specimens should be submitted to the laboratory for culture. Because the organism can be difficult to detect, identification is more likely if the specimen comes from pus from a fistula or abscess (if applicable). Isolation of *Nocardia* organisms from a gastric washing is of no significance, because *Nocardia* organisms can be present in foods. The organism can be identified on Gram's stain, with a typical appearance of delicate, gram-positive, irregularly staining, beaded, branching filaments. These filaments can fragment easily, however, into nondescript, coccobacillary forms. The organism is partially acid-fast and must be identified under oil immersion because of the extremely fine nocardial filaments (0.5–1.0 μm in diameter). It does not stain on hematoxylin-eosin and will be missed unless special tissue stains are per-

formed. Expectorated sputum may or may not yield positive smears or cultures in established pulmonary infection, and various invasive procedures including bronchoscopic biopsy, percutaneous lung aspiration, and open lung biopsy have a very high yield. Serology and skin test have previously been unreliable; however, a new antibody test with promise has been described. Unfortunately, this test has not been widely utilized.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the initial treatment for nocardiosis infection. TMP-SMX is well absorbed and is distributed in most bodily tissues. TMP-SMX inhibits *N. asteroides*, a species which commonly infects immunosupressed patients. TMP-SMX is usually well tolerated; adverse effects, however, can occur, including nausea, vomiting, anorexia, and diarrhea. Because of these adverse effects and the increase in bacterial resistance, the future use of TMP-SMX may be limited. Several successful alternative treatments have been reported (see references). Tetracycline derivatives (e.g., minocycline) have effectively and safely treated nocardiosis, especially in patients who have received transplants. Other drugs such as amikacin and imipenem show promising initial results as alternate agents. Other drugs used in the past may show effectiveness with species-targeting research. These drugs include cycloserine, ampicillin, chloramphenicol, and a combination of ampicillin and erythromycin.

Because nocardial infections are susceptible to relapses, long-term therapy is prudent. Immunocompetent patients should be treated for a minimum of 6 to 12 months. Immunosupressed patients should be treated for a minimum of 12 months with the possibility of an ongoing suppressive regimen.

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41. CRYPTOCOCCOSIS AND ACTINOMYCOSIS

Antonino Catanzaro

Cryptococcus neoformans is a unimorphic fungus that produces a granulomatous disease in humans known as *cryptococcosis*. The organism occurs as a single-budding yeast and has a thick capsule that is responsible for its characteristic visualization by India ink. The major environmental reservoir appears to be avian, primarily pigeons.

Consequently, cryptococcosis is primarily an urban infection; however, the epidemiology is becoming more complex.

Cryptococcus neoformans enters the body by the respiratory tract. No evidence indicates human-to-human transmission. In immunocompetent individuals, two thirds of infections are confined to the lungs. Cryptococcal infection in the lung can lead to (a) subpleural fibrotic nodules, usually less than 1 cm in diameter; (b) *torulomas* or larger granulomatous lesions up to 6 cm or more in diameter, which are often gelatinous and can undergo central necrosis and cavitation; (c) poorly defined or *infiltrative* masses; or (d) miliary dissemination to both lungs, resulting in diffuse edema, necrosis, and hemorrhagic exudate filling the alveoli and airways. Microscopically, the organism provokes primarily a histiocytic and giant-cell reaction. Usually, it is readily identifiable in tissue with special stains (periodic acid-Schiff, alcian blue, mucicarmine), but may not be obvious on hematoxylin–eosin-stained sections.

The clinical manifestations of pulmonary infection vary considerably. Some speculate that asymptomatic lung infection occurs frequently; however, the lack of a reliable epidemiologic tool (e.g., skin test) makes this difficult to prove. Symptoms, which can be acute or subacute, include cough, sputum (rarely bloody), chest discomfort, and low-grade fever. Pulmonary infection, however, is often asymptomatic. Physical examination may reveal rales, rhonchi, and signs of consolidation.

The risk of dissemination is greatest in individuals with underlying diseases that depress cell-mediated immunity (e.g., acquired immunodeficiency syndrome [AIDS], Hodgkin's disease, lymphoma, leukemia, sarcoidosis, and steroid treatment). With the increase in the numbers of immunocompromised patients, particularly with the AIDS epidemic, this category of patients has increased dramatically. Of disseminated cases, 75% occur in individuals with the human immunodeficiency virus (HIV) infection.

Roentgenographic abnormalities generally appear as single or multiple masslike lesions (often mimicking primary bronchogenic carcinoma). These lesions are usually peripheral, most frequently in the lower lobes. They can cavitate (10% to 15%) and become secondarily infected with other fungi or, rarely, with tuberculosis. Roentgenographic abnormalities may also appear as multiple nodular densities, larger than miliary lesions, but not clearly demarcated; confined to a segment or widely disseminated; or as single or multiple patchy infiltrative lesions. A tiny minority develop a *primary complex*, consisting of a pulmonary lesion and hilar node involvement, as seen with tuberculosis. Pleural effusion uncommonly occurs, in conjunction with a parenchymal lesion, or as an isolated finding. The effusions are exudative with a primarily lymphocytic cellular response.

The diagnosis of *C. neoformans* infection is confirmed by demonstrating the organism in body fluids or tissue. Positive cultures, however, can be difficult to obtain from sputum, cerebrospinal fluid, or blood. *C. neoformans* antigens can be identified using the latex agglutination test, but a positive test can also be present in colonized individuals without disease. Despite this problem, cryptococcal antigen is the primary tool used to diagnose patients in the appropriate clinical setting and to follow the response to treatment.

The incidence of cryptococcal infections is increasing, but, fortunately, several new treatments are now available. Currently, the treatment of choice is systemic amphotericin (0.3 mg/kg/d) and 5-flucytosine (150 mg/kg/d administered every 6 hours). However, flucytosine is converted to 5-fluorouracil and significant toxic reactions can occur. Flucytosine serves as an adjuvant therapy only, because resistance develops when it is used alone. Fluconazole and itraconazole are active against *C. neoformans*, but are less effective than amphotericin B. The lipid-based form of amphotericin B can be an effective alternative to fluconazole as a second-line prophylactic. The combination of fluconazole and 5-flucytosine continues to be studied. One study recently conducted by the California Collaborative Treatment Group showed that the efficacy of fluconazole might be enhanced when paired with flucytosine. This combination with high doses of fluconazole showed initial response rates of 70%.

Fluconazole has been found to be successful as initial therapy for cryptococcosis in patients with AIDS. As an alternate treatment, patients with AIDS can tolerate amphotericin B in lipid emulsion if the dosage is snot higher than 1 mg/kg. In patients who are severely immunocompromised, most notably those with AIDS, maintenance therapy is

needed to prevent recurrence. Maintenance therapy with fluconazole is highly effective in preventing recurrence. In patients with AIDS-associated cryptococcal meningitis, fluconazole was shown to be more effective for maintenance therapy than itraconazole.

Actinomyces israelii, the organism causing human actinomycosis, is a gram-positive, usually non–acid-fast, anaerobic organism that is often considered with fungi because of its morphology; however, its responsiveness to antibiotics and its cell-wall composition establish it as a true bacterium. Pulmonary infection is thought to be caused by aspiration of organisms residing around carious teeth. The incidence appears to be greatest from age 11 to 20 years and from 35 to 50 years, corresponding to the time when infection is more common in teeth and tonsils.

Men are affected more often than women, but no occupational or environmental predisposition is seen. In humans, the organism can cause disease in the mandibulofacial area, intestinal tract, and lung, in decreasing frequency.

Pulmonary disease can be isolated to the lung (primary) or can result from local extension, either from below the diaphragm or from the mandibulofacial area. Pathologically, infection results in a chronic granulomatous infiltrate, often with abscess formation. The organism is usually obvious on hematoxylin-eosin stain, forming a mass of filamentous hyphae staining densely with hematoxylin. Pleural extension with resultant empyema is a frequent complication of primary pulmonary actinomycosis; rarely, secondary bacterial infection can complicate empyema.

Clinically, pulmonary actinomycosis can present with cough, often productive of purulent or blood-tinged sputum; chest pain and fever. Chest-wall swelling can occur and, rarely, cutaneous abscesses or frank bronchocutaneous fistulas can develop.

Examination may reveal rales, signs of consolidation or pleural effusion, and digital clubbing. Roentgenographically, actinomycosis can present acutely with a diffuse alveolar-filling process typical of any other acute bacterial pneumonia. Alternatively, chronic infection can appear as a large mass, resembling bronchogenic carcinoma, which may extend across fissures or into the pleural space or chest wall, where it can create a soft-tissue mass or cause rib destruction. Extensive pulmonary fibrosis has been noted in a few patients with chronic infection. Extrapulmonary extension to the pericardium, mediastinum, pulmonary arteries, and beneath the diaphragm is a recognized complication of pulmonary infection. Hematogenous dissemination is rare.

The diagnosis of actinomycosis is based on demonstration of the organisms in tissue or pleural fluid. Improvements in the ability to characterize pulmonary lesions radiographically, obtain tissue by transbronchial or percutaneous biopsy, and, most recently, ultrasound-guided fine-needle aspiration have been helpful in making a specific diagnosis of this difficult disease. Radiographs demonstrating lesions with *ring enhancement* and other findings are suggestive of thoracic actinomycosis. The presence of sulfur granules (white or yellow, 1- to 2-mm clumps of mycelia) in sputum or in drainage from a sinus tract is highly suggestive of the diagnosis; however, cultural confirmation is required.

Penicillin in large doses and for long duration is the treatment of choice. Administration should be intravenous for the first 4 to 6 weeks, followed by oral administration for 12 to 18 months. Other effective alternatives are tetracycline and clindamycin. Recent reports described successful outcomes of treatment (in one patient) with a third-generation cephalosporin and (in a series of patients) with imipenem-cilastatin. Suppurative lesions should be excised or, as in the case of empyema, drained. Surgical debridement of soft-tissue lesions is believed by some to be of critical importance. Appropriate therapy yields an approximate 80% recovery rate.

Cryptococcosis

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A prospective study in 220 immunocompromised patients (188 with HIV infection, 32 with other causes of immunosuppression) undergoing BAL for fever and pulmonary symptoms led to the eventual diagnosis of cryptococcal pneumonia in 8 patients. All 8 patients had a cryptococcal antigen titer greater than or equal to 1:8. Four patients without cryptococcal pneumonia had cryptococcal antigen titers of 1:8; none had higher titers. For a cryptococcal antigen titer of greater than or equal to 1:8, findings were 100% sensitivity, 98% specificity, a positive predictive value of 67%, and a negative predictive value of 100%. The measurement of cryptococcal antigen in the BAL can be a rapid, simple way to make a diagnosis of cryptococcal pneumonia in immunosuppressed patients with pneumonia.

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In this study, 608 patients who had ultrasound-guided lung aspirations were reviewed retrospectively, and 9 aspirates documenting pulmonary cryptococcosis were collected. Five patients also underwent bronchoscopy and biopsy. The diagnostic yield with needle aspiration was greater than that of bronchoscopy.

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The most common finding is a poorly marginated nodule or mass. Lobar or segmental parenchymal opacities and, less commonly, a diffuse scattered nodular or reticulonodular pattern have also been observed. Associated adenopathy, pleural effusions, and cavitation are uncommon, occurring chiefly in immunocompromised patients.

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Cryptococcal disease most frequently involves the lungs and central nervous system. Management remains controversial, especially in patients with life-threatening disease and those with underlying T-cell dysfunction caused by AIDS, neoplasia, or corticosteroid therapy. Although amphotericin B, usually in combination with flucytosine, generally is recommended as primary therapy for patients with severe forms of disease, especially cryptococcal meningitis, alternative treatment regimens have been developed or are under investigation.

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Of 84 patients initially enrolled, 16 (19%) were found to have silent, persistent infection on the basis of cultures that became positive after entry into the study; 7 other patients were lost to follow-up shortly after entry. Of the remaining 61 patients, 10 of 27 assigned to placebo (37%) and 1 of 34 assigned to fluconazole (3%) had a recurrence of cryptococcal infection (difference in risk, 34%; 95% confidence interval, 15% to 53%). Of the 11 recurrent infections, 7 were detected in urine obtained after prostatic massage. Four meningeal infections recurred in the patients taking placebo, but none in those taking fluconazole (mean duration of follow-up, 164 days) (P = 0.03). In patients with AIDS, silent, persistent infection is common after clinically successful treatment for cryptococcal meningitis. Maintenance therapy with fluconazole is highly effective in preventing recurrent cryptococcal infection.

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A multicenter, randomized trial that compared oral fluconazole (200 mg/d) with intravenous amphotericin B (1 mg/kg of body weight per week) in patients with AIDS who had completed primary therapy for cryptococcal meningitis with amphotericin B (≥15 mg/kg) is presented. After a median follow-up of 286 days, 14 of 78 receiving amphotericin B (18%) and 2 of 111 assigned to fluconazole (2%) had relapses of symptomatic cryptococcal disease (P < 0.001 by Fisher's exact test). Serious drug-related toxicity was more frequent in the amphotericin B group (P = 0.02), as were bacterial infections (P = 0.004) and bacteremia (P = 0.002). Fluconazole taken by mouth is superior to weekly intravenous therapy with amphotericin B to prevent relapse after primary treatment with amphotericin B.

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42. NEMATODE AND TREMATODE DISEASES OF THE LUNG

Richard T. Mahon and Dennis E. Amundson

Infections from nematodes (roundworms) or trematodes (flat worms) cause helminthic pulmonary diseases. Both types of parasites are metazoan worms, a group that also includes cestodes (segmented worms). Helminthic infection is ubiquitous in nature; however, human helminthic lung disease is relatively infrequent in North America. The parasites can reach the lungs via hematogenous spread or via direct migration. The pulmonary manifestations of infection range from an asymptomatic state to catastrophic disease caused by the parasites themselves or by the host's immune response. For example, Löffler's syndrome (discussed below) is the result of the host's response to any of several helminthic infections that migrate through the lung during their life cycles.

The pathologic nematodes include *Ascaris*, hookworm species, *Strongyloides* and *Filaria*. *Ascaris lumbricodies* is one of the most common intestinal nematodes in the world. Found predominately in the tropics, it also infects up to 4 million people living in the southern United States, especially in rural areas. Humans are infected by ingestion of contaminated soil or food that contains the ascaris egg that then hatches in the gastrointestinal tract. The larvae subsequently migrate via the venous system to the right ventricle and to the lungs where they enter the alveoli and ascend the tracheobronchial tree.

Pulmonary disease results from a hypersensitivity response to migrating larvae. The manifestations are usually limited to transient pulmonary infiltrates and peripheral eosinophilia. A few patients develop all the stigmata of Löffler's syndrome: cough, dyspnea, wheezing, sternal pain, and mild hemoptysis associated with fever. Secondary bacterial pneumonia is common and mechanical airway obstruction has been described when a high worm burden is present.

Eosinophilia and elevated serum IgE levels are common. Chest radiographs may show patchy consolidation or diffuse miliary infiltrates. Sputum is rich in eosinophils and in crystallized protein from fragmented eosinophils (Charcot-Leyden crystals). Eggs are rarely found in the sputum. In the correct clinical setting, the diagnosis can be made by demonstration of ascaris eggs in the stool. Unfortunately, the ova in stool specimens may not be manifested for up to 40 days after the initial presentation.

The hookworms, *Ancylatoma duodenale* and *Necatar americanus*, infect humans through direct penetration of skin by the infective larvae found in moist contaminated soil. The geographic distribution is worldwide and includes the southeastern United States (*N. americanus*). As with ascaris, the hookworm larvae migrate to the lung via the venous system and can produce a self-limited Löffler's syndrome before they inhabit the small intestine. Also similar to ascariasis, the stool examination may not be positive for up to 2 months after the pulmonary symptoms develop. Treatment for pulmonary symptoms is generally not necessary but eradication of the parasite can be achieved with mebendazole.

Strongyloides stercoralis is endemic in tropical and subtropical areas and in the southeastern United States. A relatively unique feature of *S. stercoralis* is its ability to complete its life cycle entirely within the human; the host may, therefore, develop a substantial worm burden. Although the acute and chronic stages generally produce only mild symptoms in normal hosts, in immunocompromised conditions (acquired immunodeficiency syndrome [AIDS], steroids, and malignancy), it can be devastating. Strongyloides migrate hematogenously to the lungs after the larvae penetrate the skin. From here, they ascend the tracheobronchial tree and are swallowed. In the duodenum, they mature and produce larvae, some of which can penetrate the colonic mucosa or perianal skin.

The initial skin penetration by *S. stercoralis* may be manifested by local inflammation; edema and a serpiginous erythematous track rarely come to medical attention. The gastrointestinal manifestations include duodenitis, abdominal pain, and malabsorption that can be seen with high worm burdens. The pulmonary manifestations in the immunocompetent include cough, wheezing, and a recurrent pneumonitis. Peripheral blood eosinophilia may not be present. Asthma induced by chronic strongyloides paradoxically will worsen with corticosteroid administration.

In the immunocompromised host (usually with corticosteroid use), the colonic penetration of filariform larvae occurs unchecked and can widely disseminate to lungs, liver, central nervous system, and other organ symptoms. The so-called *hyperinfection syndrome* carries an extremely high mortality. The pulmonary manifestations at this stage include adult respiratory distress syndrome (ARDS), or secondary bacterial infections. Interestingly, the hyperinfection syndrome is less common in individuals infected with the human immunodeficiency virus (HIV) in endemic areas than one would predict. Also curious is the observation that cyclosporine in transplant patients may have a theoretical protective effect.

The diagnosis of strongyloides infection rests on finding larvae by stool examination or a duodenal *string test*; however, these tests lack adequate sensitivity. Enzyme-linked immunosorbent assays (ELISA) carry a sensitivity of approximately 90% with a negative predictive value of 95%. In hyperinfection syndrome, strongyloides has been diagnosed by examination of sputum or cerebral spinal fluid. Thiabendazole or invermectin are treatment options.

Infection by members of the *Filaria* superfamily (filiariasis) can be asymptomatic, but can also cause acute or chronic tropical pulmonary eosinophilia (TPE). TPE is a relatively uncommon manifestation of human filarial disease (mostly seen with *Wuchereria bancrofti* and *Brugia maylayi*) and is most common in India, Southeast Asia, and Sri Lanka. TPE is considered to be a hypersensitivity reaction to filaria antigen. In the acute phase, TPE causes paroxysmal cough, wheeze, pulmonary infiltrates, marked peripheral eosinophilia, elevated IgE, and an eosinophilic alveolar exudate. The chest radiograph shows fluffy reticulonodular shadows in the mid and lower lung zones; a miliary pattern has also been described. Up to 20% of patients may have normal radiographs. Some patients develop chronic TPE, manifested by a restrictive fibrotic pulmonary process and without peripheral or alveolar eosinophilia.

Most patients with acute TPE respond to diethylcarbamazine (6 mg/kg for 21 days), but relapse (or re-infection) and chronically unresponsive disease are well described. Other treatment options included thiabendazole and ivermectin. Concurrent corticosteroids may be useful. The clinical response to therapy is poor in chronic disease.

Dirofilaria immitis (dog heartworm) can be transmitted to the human via a mosquito vector and has been reported increasingly in the United States. In dogs and cats, the larvae develop into sexually mature worms that travel to the right ventricle. In the human host, larvae cannot mature; they die, but are passively transported to the lung via the venous system. The infection generally manifests itself as an asymptomatic pulmonary nodule, but can present with cough, chest pain, and hemoptysis.

Toxocariasis (visceral larvae migrans) is caused by human infection with a dog or cat ascarid. Endemic to North America, England, Australia, and Mexico, *Toxocaris canis* and *T. cutis* eggs are ingested from contaminated soil and food. As is the case with dog heartworm, the human is an imperfect host and maturation of the larvae cannot occur. The eggs hatch in the gut and the larvae migrate through host tissue. This migration causes an inflammatory granulomatous response that is considered the source of clinical manifestations of the disease. Symptoms are a manifestation of infection extent. Viseral larva migrans is generally asymptomatic but can have a fulminant course with central nervous system involvement, acute pneumonia, or severe asthma.

Infection is most common in children (especially those with pica) and can be associated with cough, wheezing, and pulmonary infiltrates. Peripheral eosinophilia is marked and hepatosplenomegaly may be present. A definitive diagnosis hinges on the demonstration of larvae in tissue; however, an ELISA to antitoxocara antibodies and specific larva-related IgE tests are useful. Examination of stool for eggs is useless, as the ascarid cannot reproduce in the human host.

Generally, the disease is self-limited and treatment is generally not indicated; however diethylcarbazine or thiabendazole is recommended if drug treatment is necessary. The use of corticosteroids in severe cases has been associated anecdotally with clinical improvement.

Two types of trematodes (flat worms) can cause human infection: schistosmiasis and paragonimiasis. Schistosomiasis is a digenetic parasitic trematode that infects an estimated 200 million people worldwide. Five species can cause human disease: (a) *Schistosoma japonicum*, the most common cause of infection, found in Japan, China, and the Philippines; (b) *S. mansoni*, found in Africa, Arabia, and South America; (c) *S. haematobium* found in Africa and the Middle East; (d) *S. intercalatum*, found in western Africa; and (e) *S. matthei*, a species found in South Africa that rarely causes infection in humans. Infection occurs through contact with fresh water that contains infective cercariae released from snails, the intermediate hosts. The cercariae penetrate the intact skin of the *definitive* mammalian host and undergo transformation into migrating schistosomulum larvae. Mature adults localize in mesenteric (*S. mansoni* and *S. japonicum*) or bladder vesicle venules (*S. haematobium*). From here, eggs are carried via the portal system to the liver and then into the venous system, arriving in the lungs via the right side of the heart approximately 1 week after the initial infection.

Pulmonary manifestations generally entail an acute illness followed by chronic sequelae that can include pulmonary hypertension. Acute symptoms are seen a few weeks after infection, generally in a previously unexposed individual. The patient may have symptoms resembling serum sickness (e.g., fever, chills, abdominal pain, urticaria, and myalgias); physical findings include hepatomegaly, lymphadenopathy, and peripheral

eosinophilia. The patient may have a cough or wheeze, whereas the chest radiograph may disclose fine infiltrates or micronodules. Diagnosis by serum antischistosomal antibodies or the detection of eggs in stool is possible. The syndrome has been reported with all schistosomes, but may be more common with *S. japonicum*, which has a higher egg secretion rate. The pathogenesis is thought to be immune complex deposition secondary to the release of eggs. The syndrome is usually self-limiting but the course can be abbreviated with corticosteroids and praziquantel.

Schistosomiasis can cause pulmonary hypertension if chronic hepatosplenic disease leads to portal hypertension and portosystemic shunting. The lungs undergo a continuous embolic assault from the infected gut and the eggs lodge in the pulmonary arterioles, producing a granulomatous pulmonary endarteritis with resulting pulmonary hypertension. Because this develops only in those who have marked hepatic involvement, the diagnosis can be established by liver biopsy that demonstrates *Symmer's pipestem fibrosis*. Eggs in transbronchial biopsies have also been shown. At this stage of illness, antischistosomal therapy yields minimal clinical improvement.

In both pulmonary manifestations of schistosomiasis, therapy can result in embolization of the adult worm from the liver to the lungs, causing a self-limited syndrome of cough, wheeze, radiographic infiltrates, and a rise in peripheral eosinophil count.

Paragonimiasis is a disease with a widespread geographic range that is caused by the trematode *Paragonimus*. The best known species (also with the widest distribution) is *P. westermani*, which is prevalent in Asia, India, and Africa. Humans become accidental hosts by consuming uncooked crustaceans that harbor the larvae of this lung fluke. Once ingested, the larvae penetrate into the peritoneal cavity and migrate through the diaphragm and pleura into the lung. Here, they mature and produce eggs that are either expectorated or swallowed. Unlike most other helminths, the pulmonary involvement of paragonimiasis is essential in the fluke's development. Early infection can cause pleuritic chest pain, with unilateral small to massive eosinophilic pleural effusions. As time passes, fleeting infiltrates and pulmonary hemorrhage may be seen.

Once in the lungs, the larvae become encysted and eggs are produced. Clinically, this stage of infection can last for several years and carry few symptoms. Rupture of the cysts will cause blood-streaked sputum containing parasite eggs, necrotic tissue, and Charcot-Leyden crystals. Radiographically, small cavitary nodules, ring shadows, and masslike lesions may be present in addition to bilateral pleural effusions. A peripheral eosinophilia is generally present and the pleural fluid is exudative and eosinophilic. When eosinophilia is not present, it is common for paragonimiasis to be confused with tuberculosis.

The diagnosis is established by demonstration of parasitic eggs in sputum, feces, pleural fluid, or tissue. A single sputum examination has a sensitivity of 30% to 45% and the yield is increased with multiple collections. Stool examination is generally less sensitive than pleural fluid analysis. ELISA and immunoblotting assay techniques can also help make the diagnosis. The first-line therapy is with praziquantel.

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43. AMEBIASIS AND ECHINOCOCCAL DISEASES OF THE LUNG

William L. Ring

Amebiasis is caused by the protozoan *Entamoeba histolytica* and is most common in tropical and subtropical regions. In the United States, infection is observed most commonly in (a) travelers and immigrants exposed in endemic areas; (b) patients in mental health institutions; (c) human immunodeficiency virus (HIV)-positive patients; and (d) sexually active male homosexuals. The organism is usually confined to the colon, producing either no symptoms or amebic dysentery. The disease is usually contracted by ingestion of food or water contaminated by feces or by fecal-oral contact.

Rarely, mature organisms (trophozoites) penetrate the bowel wall and migrate to the liver by the hepatic veins, where an abscess may form. This invasive form of amebiasis is three to ten times more common in men, is associated with alcohol abuse, and is more common in individuals who are malnourished or immunosuppressed. Most patients with invasive disease present with several weeks of right upper quadrant abdominal pain and fevers. By the time a hepatic abscess forms, no dysenteric symptoms are

present in up to two thirds of patients and most patients do not have parasites detectable in their stool.

Thoracic involvement occurs in 13% to 35% of patients with hepatic amebiasis. The usual route of pleuropulmonary infection is by extension from a hepatic or subdiaphragmatic abscess. Less commonly, direct parasitic migration occurs into the thorax. In addition, hematogenous spread to the lung rarely occurs by hemorrhoidal veins or lymphatics. All modes of spread can result in empyema or lung abscess. Pleuropulmonary disease can also occur without actual parasitic invasion in the form of lower lobe infiltrates and exudative effusions; the mechanism for this is not clear, but it is presumably a response to subdiaphragmatic infection.

Amebic pleuropulmonary disease is 10 to 15 times more common in men than in women, with a peak incidence between ages 20 and 40 years. Patients usually have a history of amebic dysentery and may complain of right upper quadrant pain, weight loss, and cough. Rarely, the cough is productive of thick, dark *chocolate sauce* or *anchovy paste* sputum or even bile (biloptysis), indicating hepatobronchial and bronchobiliary fistulas, respectively. Fever and signs of empyema or consolidation may also be present. Chest roentgenogram typically reveals a right-sided effusion or right lower lobe lung abscess. In addition, areas of consolidation may be seen in the right lower lobe, middle lobe, or both. The right diaphragm may be elevated and have decreased motility. In cases involving the left lobe of the liver, changes can occur in the left lung field. Computerized tomography will show the liver abscess. Magnetic resonance imaging can directly visualize the secondary diaphragmatic rupture. Thoracentesis usually reveals a sterile exudate; however, organisms are rarely present. Routine laboratory examination may show a mild leukocytosis and eosinophilia. Cysts are rarely found in the sputum or the pleural fluid; however, when present, they confirm the diagnosis. A serum hemagglutination test for antibodies to amebae is positive in up to 95% of invasive infections, but will remain positive for years after the infection.

In the appropriate clinical picture, it is reasonable to initiate therapy. Metronidazole (750 mg tid) orally for 10 days followed by a luminal agent such as iodoquinol (650 mg tid for 20 days), paromomycin (25–35 mg/kg/d in 3 divided doses for 7 days), or diloxanide furoate (500 mg tid for 10 days) is generally recommended for extraintestinal amebiasis. Failure to respond to treatment should call into question the diagnosis or suggest the possibility of a secondary, bacterial infection. The rare patient with invasive amebiasis who does not respond to this regimen should be treated with chloroquine and percutaneous drainage of the liver abscess and any pleural fluid. Surgery is rarely indicated.

Echinococcosis or hydatid disease is caused by the postlarval metacestode stage of the tapeworm *Echinococcus*. Humans are an intermediate host for this parasite. After ingestion of contaminated food, water, or soil, the oncosphere migrates via the portal circulation, whereby it is ultimately deposited within an organ. Once in an organ, cellular differentiation occurs, resulting in the development of a cyst. The mature cyst consists of an inner germinal layer, the endocyst; an outer chitinous layer, the exocyst; and a peripheral fibrous layer caused by host reaction, the pericyst. Four species of *Echinococcus* cause human disease. *Echinococcus granulosus* is the most common one because of its wide distribution and its high prevalence in sheep; it involves the lung 60% of the time, and often has a protracted and relatively benign course. *E. granulosus* causes cystic echinococcosis, the classic hydatid disease, with often large, unilocular cysts. *E. multilocularis* is less common; it is primarily a liver disease with occasional involvement of the lung, and typically has an aggressive, malignant course. *E. multilocularis* causes alveolar echinococcosis, with somewhat smaller, multilocular cysts, which at pathology appear to have an alveolar appearance. *E. vogeli* and *E. oligarthus* are restricted to parts of Central and South America and only rarely cause human disease. They cause polycystic echinococcosis.

Echinococcus granulosus is endemic in sheep-raising regions of the Mediterranean, Russia, Australia, and parts of South America and Africa. In North America, it has been reported in both Canada and the United States, particularly in the Mississippi River Valley and Alaska. Dogs and other carnivores serve as the definitive hosts, whereas humans, sheep, and cattle are intermediate hosts. Pulmonary hydatid cysts are typically 1 to 10 cm in diameter, but can grow much larger. The cysts usually grow at a rate of 1 cm/y in diameter, but growth rates of up to 5 cm/y have been reported. The cysts are usually located in the lower lobes, and are twice as frequent on the right.

When multiple (20% to 30%), they are most often unilateral (80%). A cyst can rupture into the bronchial tree, in which case the fluid is replaced with air, or into the pleural space. Pulmonary cysts often (10% to 60%) coexist with hepatic cysts. Clinically, most patients are asymptomatic. Hydatid cysts are discovered most frequently on routine chest radiographs. Cough, hemoptysis, and chest pain occur uncommonly. Mediastinal cysts can erode into adjacent structures, causing bone pain, hemorrhage, or airflow obstruction. Uncommonly, rupture of a cyst, either spontaneously or during surgery, can result in an acute hypersensitivity reaction. Roentgenographically, the cyst(s) appears as a dense, well-circumscribed oval or spherical mass, which can reach enormous dimensions and fill an entire hemithorax. Debris within the fluid of the cyst, which is called *hydatid sand*, has typical characteristics. If bronchial communication has occurred, air between the pericyst and exocyst can produce the appearance of a thin layer around the cyst—the meniscus or moon skin sign. Air penetrating the interior of the cyst may outline the inner surface of the exocyst, producing parallel arches of air—Cumbo's sign. As air fills the space, the endocyst and the exocyst may detach, showing an irregular air fluid layer with the collapsed membranes floating on the fluid surface; this is known as the water lily, lotus on water, or camelot sign. Calcification of the cyst is rare. Eosinophilia, usually not prominent, is found in less than 50% of patients. A skin test (Casoni) for delayed hypersensitivity to cyst material is generally positive but does not correlate with disease activity. A number of sensitive, serologic tests are available, but they are of limited clinical value because of poor specificity. Fiberoptic bronchoscopy may reveal whitish-yellow gelatinous material in the bronchi. Conclusive diagnosis can be made if components of the hydatid cysts, including possibly scolexes or degenerated hooklets, are identified in bronchoalveolar-lavage fluid, pleural fluid, or sputum. Although some risk is seen to percutaneous aspiration of a cyst, some studies have suggested that this can be done safely. Traditionally, the treatment of choice has been surgical resection. Some studies have suggested that medical treatment alone with a benzimidazole (albendazole or mebendazole) can be a safe, initial strategy.

Echinococcus multilocularis is endemic in an area extending from the White Sea to the Bering Straits, including the former Soviet Union, the European alpine countries, southern and central Canada, northeastern United States, Alaska, Japan, and China. The red fox, Arctic foxes, coyotes, and wolves are the definitive hosts, and certain wild rodents are intermediate hosts. The infection originates from larval penetration through the duodenal wall and transit via the portal vein. Most are trapped in the hepatic sinusoids, but some larvae pass through and are subsequently trapped in the alveolar capillaries. Cysts can form in the liver, the lung, or in both organs. Progressive larval invasion to contiguous regions as well as occasional metastases to distant sites leads to massive tissue destruction. When the lung is involved by direct invasion from the diseased liver, typically only the right lower lung field is abnormal, often appearing roentgenographically as an abscess. With hematogenous spread, multiple small cysts can form diffusely in the lung. Typically, pulmonary symptoms are overshadowed by hepatic dysfunction. Serological testing, particularly the Em2-ELISA, is both sensitive and specific and is useful both to assist in the diagnosis of the disease and to monitor for recurrence. Alveolar echinococcosis is uniformly fatal if not treated. In cases with limited disease, radical hepatic resection can lead to cure. Prolonged drug therapy with mebendazole or albendazole has a significant impact on disease progression and may achieve a cure.

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44. *PNEUMOCYSTIS CARINII* PNEUMONIA AND OTHER PULMONARY INFECTIONS AND COMPLICATIONS IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS

Mark L. Metersky

During the past several years, extraordinary improvements in the prognosis of patients infected with the human immunodeficiency virus (HIV) have been achieved. These advances chiefly occurred because of the widespread use of effective modes of prophylaxis for various opportunistic infections and the discovery of protease inhibitors as a component of highly active antiretroviral therapy (HAART). Nonetheless, infectious and noninfectious pulmonary complications of HIV infection remain frequent causes of morbidity and mortality. For example, although prophylaxis for *Pneumocystis carinii* pneumonia (PCP) is both successful and widely used, PCP remains an important cause of pulmonary disease in patients infected with HIV. Therefore, the clinician must have a logical approach to a HIV-infected patient with undiagnosed lung disease so that an efficient diagnostic workup can be undertaken and appropriate empiric therapy can be instituted.

Although its incidence has declined in recent years, PCP remains common among patients with acquired immunodeficiency syndrome (AIDS), especially those who have been noncompliant with chemoprophylaxis, or who are unaware of their HIV infection. The biology of the organism remains poorly understood because of the inability to culture it. It was initially classified as a protozoan on morphologic grounds, but studies of its small ribosomal unit RNA sequences indicate that *P. carinii* is a fungus. Infection is thought to be via inhalation, and serologic studies indicate that approximately 85% of persons are infected in early childhood. However, both the inability to identify *P. carinii* in the lungs of healthy immunosuppressed individuals and well-documented case clusters cast some doubt on the theory that clinical disease results from reactivation of latent primary infection. The risk of PCP in a person infected with HIV increases sharply once the absolute CD4 lymphocyte count drops to less than 200, and the risk with any CD4 cell count is increased by the presence of chronic HIV-associated symptoms such as fever or thrush. Finally, the annual risk of recurrence after an episode is greater than 60%. Therefore, all HIV-infected persons with a history of PCP or less than 200 CD4 cells should receive chemoprophylaxis, and it should be considered for persons having less than 350 CD4 cells and signs of HIV infection (especially oral thrush) or a rapidly declining CD4 cell count. Several studies suggest that, with the use of HAART, patients who had previously required primary PCP prophylaxis can safely have it discontinued if the CD4 cell count rises above 200. However, insufficient information is available to recommend discontinuation of secondary prophylaxis at this time.

Trimethoprim-sulfamethoxazole (TMP–SMX) (co-trimoxazole, Bactrim, Septra) is the most active and most widely recommended drug for PCP prophylaxis. Breakthroughs in persons actually taking the drug are rare. Overall, it provides superior clinical outcomes among patients with more advanced immunosuppression or a prior episode of disease; it also affords some protection against toxoplasmosis. The strongest data support the use of one double-strength or one single-strength tablet daily. Short-term intolerance in the

form of allergic-type reactions and gastrointestinal distress affects 20% to 30% of HIV-infected persons, but these reactions are often transient and prophylaxis can frequently be continued with symptomatic therapy. For those who are truly intolerant of TMP–SMX, aerosolized pentamidine (via the Respirgard nebulizer), dapsone, or atovaquone can be used.

The onset of PCP is marked by the development of nonproductive cough, dyspnea (often only exertional), fever, and, occasionally, chest pain or chills. Atypical features such as a modestly productive cough can occur in 20% of cases. In contrast to the abrupt onset seen in patients with cancer, onset in HIV-infected patients generally occurs over 2 to 3 weeks. Signs of the patient's underlying disease (e.g., wasting or oral thrush) can dominate the physical examination, but patients are often tachypneic and, in advanced cases, breathless or even cyanotic. The lung examination is usually normal. The finding of prominent rales or consolidation should prompt consideration of an alternative diagnosis.

Leukopenia, lymphopenia, and anemia are common, and serum lactic dehydrogenase is nearly always elevated. The chest radiograph is abnormal in 80% to 90% of cases. The classic findings are diffuse interstitial or fluffy alveolar infiltrates, which are more prominent in the perihilar regions. Other radiographic appearances are also common, including normal radiographic examinations (in 5% to 10%); asymmetric infiltrates; or an apical predominance mimicking tuberculosis in patients receiving prophylactic inhaled pentamidine. Localized infiltrates and nodules can occur but more commonly represent fungal, bacterial, or mycobacterial pneumonia or Kaposi's sarcoma (KS). Thin-walled cysts or blebs are often seen on careful inspection of the radiograph. This finding, along with a history of inhaled pentamidine use, is associated with the occurrence of pneumothorax, which can be seen in 5% to 9% of patients with PCP. Conversely, patients infected with HIV who present with spontaneous pneumothorax usually have active PCP, and should be treated as such unless another diagnosis such as tuberculosis or pleural KS is found. Pleural effusion large enough to reveal more than blunting of the costophrenic angle and adenopathy also suggests an alternative diagnosis (e.g., KS or mycobacterial disease). The arterial P_{O_2} is abnormal in most cases, and is a major prognostic indicator, with survival being the rule for patients presenting with near normal oxygenation. An abnormal carbon monoxide diffusing capacity, oxygen desaturation during exercise, and an abnormal gallium lung scan are sensitive but nonspecific for PCP infection. High resolution computed tomography (CT) scan occasionally is of use—a normal study essentially rules out the diagnosis of PCP.

Because the organism cannot be cultured, staining sputum induced by the inhalation of hypertonic saline usually makes the definitive diagnosis of PCP. If induced sputum is either negative or not available, bronchoalveolar lavage (BAL) fluid obtained by fiberoptic bronchoscopy should be examined. Amplification of DNA by the use of the polymerase chain reaction is highly sensitive but is not frequently used clinically. Bronchial brushings and transbronchial biopsy generally add little to the diagnostic yield over that of BAL alone and usually need not be performed. However, in the setting of an atypical presentation (e.g., focal disease or when the patient has been receiving effective prophylaxis), other diseases become more likely and transbronchial biopsy should be considered. On standard stains, the typical histologic finding is clumps of foamy eosinophilic material in the alveolar lumen. The eosinophilic material consists of extracystic trophozoites in a proteinaceous matrix. Experienced examiners using Giemsa, Diff-Quick, or toluidine blue O stains can identify the trophozoites. However, a definitive diagnosis is most easily made by identifying cysts, which stain black on Gomori's methenamine silver stain (GMS or *silver stain*) and fluoresce on monoclonal antibody stains. The advantages of using the newer direct fluorescent antibody stain include a slightly higher sensitivity and less dependency on the experience of the technician.

Whereas the examination of bronchoalveolar lavage fluid is generally 90% to 95% sensitive for the diagnosis of PCP, the reported sensitivity of induced sputum varies widely between institutions, from under 20% to more than 90%, with most reports in the 50% to 60% range. The reasons for this variability are not completely clear but may include both technical factors as well as motivation of both the respiratory therapist and the patient. Although it has been reported that the sensitivity of examining bronchoalveolar lavage fluid is decreased in patients receiving aerosolized pentamidine,

performing the BAL in the anatomic area showing the greatest abnormality on chest radiograph may compensate for this limitation. Similarly, most studies do not suggest a decreased yield of induced sputum in patients receiving prophylaxis with inhaled pentamidine. Cysts can persist for weeks to months after successful treatment, so a positive result on repeat testing does not necessarily indicate relapse.

Therapy for PCP should begin as soon as the diagnosis has been made. In fact, presumptive therapy (before diagnostic confirmation) may be appropriate in some cases wherein a substantial clinical suspicion of PCP exists, in order to prevent the progression to more severe, life-threatening disease. Although some experts advocate entirely empiric therapy for patients with fairly characteristic clinical presentations and chest radiographs, the initial findings can be misleading and it is wise to confirm the diagnosis cytologically as soon as possible. Hospitalization is indicated for nearly all persons with alveolar-arterial oxygen differences of greater than 30 to 40 mmHg, especially those with clearly abnormal chest radiographs or very elevated lactate dehydrogenase values.

Trimethoprim-sulfamethoxazole is the preferred form of therapy, but the commonly used dosage of 20 mg/kg/d of the trimethoprim component is excessive and can exacerbate intolerance. Therapeutic levels are achieved by 15 mg/kg/d in typical patients. Parenteral therapy is preferred in moderate to severe disease and in the setting of gastrointestinal dysfunction. The recommended duration of therapy is 3 weeks. More than 50% of patients suffer adverse and frequently dose-limiting toxicity, including rash, fever, transaminase elevations, and leukocytopenia. Mild to moderate toxicity, however, can frequently be managed with antihistamines or antipyretics and may not necessitate switching therapy.

If TMP–SMX is not tolerated, a reasonable alternative is parenteral pentamidine, which has a similar efficacy. However, switching to pentamidine after *failure* of TMP–SMX (as opposed to *intolerance*) does not appear to improve prognosis. The usually recommended dosage of pentamidine is 4 mg/kg/d, given as a single daily dose. Because the drug accumulates at this dosage and total dose relates to the risk of serious toxicity, many clinicians routinely limit therapy with this agent to a 2-week course and prescribe 3 mg/kg/d, especially after the first few days of therapy or in patients with renal insufficiency. Infusions should be given over 1 to 2 hours to avoid hypotension. Intramuscular injection can be an acceptable alternative for short periods in some settings. Toxicity is less common with pentamidine than with TMP–SMX, but more often may be serious. Nephrotoxicity, pancreatitis, arrhythmia, and leukopenia can occur, but the most serious complication is pancreatic islet cell toxicity, manifested by *dysglycemia* (hyperglycemia or hypoglycemia) appearing early, late, or even after completion of therapy. The risk of dysglycemia, which can be fatal, increases to more than 10% with more than 2 weeks of therapy, in the presence of azotemia, or after other recent exposure to pentamidine.

Data indicating acceptable efficacy exist for several alternate regimens. In general, these have not yet been subjected to rigorous comparative trials and, thus, are generally reserved for persons intolerant to or failing conventional therapy. The combination of oral dapsone (100 mg/d in single or divided doses) plus trimethoprim (15–20 mg/kg/d in four divided doses) is an acceptable alternate oral regimen for sulfa-intolerant individuals. Less experience has been had with the combination of clindamycin and primaquine. Primaquine is dosed at 15 to 30 mg of base daily, whereas oral clindamycin (300–450 mg) is given every 6 hours. Persons receiving primaquine should be screened for glucose-phosphate dehydrogenase deficiency to minimize the risk of hemolytic anemia. Atovaquone (750 mg twice daily) is better tolerated than TMP–SMX or pentamidine and appears to be at least as effective as pentamidine in patients who are intolerant to TMP–SMX. Atovaquone, however, is less effective than TMP–SMX. Absorption of this drug is very erratic, and patients should eat before each dose. Trimetrexate, a potent dihydrofolate reductase inhibitor that must be given with *leucovorin rescue* to prevent serious cytoxicity, provides a well-tolerated alternative to the first-line drugs when parenteral therapy is required, but it also is less effective than TMP–SMX. Aerosolized pentamidine (600 mg/d) has been successfully used for primary therapy, but the vagaries of local drug delivery suggest that this therapy be reserved for persons with mild disease and those whose disease has improved to mild during a partial course of conventional therapy.

Administration of adjunctive corticosteroids within 72 hours after the start of antipneumocystis therapy mitigates the initial decline in oxygenation seen with the initiation of therapy in most patients. In patients presenting with partial pressures of oxygen of less than 70 mm Hg while breathing room air, this approach reduces the risk of respiratory failure and death. In contrast, late or *rescue* corticosteroids appear to confer little benefit. The best-studied regimen is prednisone (40 mg twice daily for 5 days, followed by 40 mg/d for 5 days, and then 20 mg/d for the remainder of antipneumocystis therapy), but some clinicians prefer shorter courses. Regardless of the regimen chosen, the use of adjunctive corticosteroids for PCP confers an obligation to confirm the diagnosis definitively, because other unsuspected infections (e.g., tuberculosis) could become fulminant during steroid therapy.

Pneumothoraces seen in the setting of PCP often cause major morbidity because of prolonged air leaks. Although such patients have often languished for weeks in the hospital, several studies suggest that, after a limited period of unsuccessful management by tube thoracostomy, appropriate candidates should be referred for surgical management. Evidence suggests that patients who require only tube thoracostomy may have a lower recurrence rate if chemical pleurodesis is performed.

Clinical improvement is often not seen until after 3 to 5 days of therapy in successfully treated cases of PCP, and it is premature to declare a therapy failure before that time. It does not appear that switching therapy or instituting combination therapy for clinical failures improves outcome. However, if a change in therapy is necessary, it is prudent to give both drugs until two to four doses of the new agent have been given. Mechanical ventilation is often indicated for early respiratory failure, as the duration of mechanical ventilation may be brief. More than 50% of patients survive mechanical ventilation and those who do survive have a long-term prognosis similar to others with the same level of immunosuppression. However, the prognosis is much less favorable in persons developing respiratory failure more than 5 days after initiation of treatment and in those requiring prolonged mechanical ventilation.

Patients with HIV infection often have concomitant cytomegalovirus (CMV) infection, and CMV is frequently grown from the secretions of patients with respiratory syndromes. Merely culturing the virus from pulmonary secretions has no negative prognostic implication, but many clinicians believe finding cytomegalic cells in specimens constitutes cytologic evidence of tissue disease and will treat with ganciclovir or foscarnet.

Bacterial pneumonia, which is a common complication of HIV infection, occurs more frequently than PCP in most series. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of community-acquired bacterial pneumonia in these patients. In addition, those with advanced disease, recent hospitalization, or with prior antibiotic exposure may be colonized with typical nosocomial organisms (particularly *Pseudomonas aeruginosa* and *Staphylococcus aureus*) and commonly suffer pneumonia from these bacteria. More unusual infections such as *Rodococcus equi* cavitary pneumonia or bacteremia or pneumonia caused by *Nocardia* asteroides (without prior cortico-steroid exposure) may also be seen. Although the clinical presentation of bacterial pneumonia in patients infected with HIV is similar to that seen in immunocompetent patients, bacteremia is more frequently seen. The treatment of bacterial pneumonia in patients infected with HIV is not different from treatment of patients without HIV infection and, indeed, the response to therapy and short-term prognosis differs little between the two groups.

Mycobacterium tuberculosis (MTB) is a serious threat to HIV-infected patients and those around them. Persons with concurrent HIV and MTB infection have an 8% to 10% risk per year of developing clinical tuberculosis (TB), which is extraordinary, considering that a normal person with MTB infection has a similar chance of developing tuberculosis an entire lifetime. For this reason, tuberculin skin testing and, when appropriate, TB prophylaxis are essential components in the initial care of those with HIV infection. It is important to note that the criterion for a positive tuberculin skin test is 5 mm of induration in the immunocompromised host. Prophylaxis can be accomplished by the standard regimen of isoniazid alone, although several short-course options are available. Rifampin, however, is relatively contraindicated in patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors because of drug interactions; rifabutin can be substituted in some cases.

Tuberculosis can occur as a primary infection or as reactivation of prior infection, and tends to present earlier in the course of HIV infection than most other infectious complications. Dissemination and even mycobacteremia are common. The chest radiograph presentation is dependent on the degree of immunosuppression, with typical apical infiltrates being most common among patients with normal or mildly diminished CD4 cell counts. As immunosuppression progresses, cavitation becomes rare, whereas nonapical and diffuse infiltrates predominate. Alarmingly, some patients can present with normal radiographs or only hilar and mediastinal adenopathy, yet have the organism in their sputum. Diagnostic strategies for TB in patients with AIDS are similar to those in patients without AIDS (Chapter 33): typically through examination of sputum, bronchoalveolar lavage fluid, or transbronchial biopsy. Likewise, standard antituberculous drug regimens are effective for treatment of HIV-associated TB. However, the initial use of four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) and sensitivity testing is mandatory because of the emergence of multidrug-resistant MTB (MDR-TB) in HIV-infected persons. For example, in one study, one third of isolates found in New York City were resistant to one drug and one fifth were resistant to both isoniazid and rifampin. Interestingly, initiating HAART in patients with AIDS during treatment for TB can be associated with temporary worsening of TB signs and symptoms, because of the development of more vigorous immune responses.

Infection with *Mycobacterium avium complex* (MAC) organisms occurs in 25% to 50% of patients with advanced HIV disease, but is rarely seen in patients with a CD4 cell count greater than 50. Constitutional symptoms are common on presentation, and widespread seeding of the blood, liver, and bone marrow occurs frequently. Although MAC is commonly cultured from pulmonary secretions, it is quite rare for it to cause pulmonary signs or symptoms. This is in contrast to some other atypical mycobacteria such as *M. kansasii*, *M. gordonae*, and *M. xenopi*, all of which can cause pulmonary disease.

The HIV-associated fungal pneumonia caused by *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Coccidioides immitis* commonly presents as part of a syndrome of disseminated disease in persons with very advanced HIV infection. Most invasive fungal infections in HIV disease are caused by *C. neoformans* infection, which is seldom seen in persons with CD4 counts of more than 75 to 100 cells/μL. Cryptococcal pneumonia is invariably accompanied by antigenemia and usually by widespread infection, including meningitis. The chest radiograph often shows diffuse abnormalities, but focal masslike infiltrates, masses, and effusions can be seen. Amphotericin B, with or without flucytosine is used for treatment. Milder cases may respond to fluconazole. Maintenance therapy with fluconazole is required after recovery.

Histoplasmosis can occur, either by primary *H. capsulatum* infection in endemic areas or by reactivation (often long after compromised persons have moved from these areas). Up to half of patients with progressive disease will have complaints of cough or dyspnea at diagnosis, and two thirds will have organisms detectable in pulmonary secretions. However, other focal complaints, constitutional symptoms, or a sepsislike syndrome can dominate the clinical picture. Response to amphotericin B is usually prompt. After recovery, long-term maintenance therapy is required; itraconazole is the preferred agent.

Coccidioidomycosis (*C. immitis* infection) can occur in some areas of the southwestern United States. In fact, the 3-year risk of coccidioidomycosis in HIV-infected patients residing in high prevalence areas can be as high as 25%. Focal pulmonary disease occurs in approximately 25% of cases. Coccidioidomycosis in non–HIV-infected patients typically presents with cavitary disease, but infiltrates, nodules, and adenopathy are more common in patients with AIDS. Diffuse pulmonary disease occurs in approximately 40% of cases. Chest radiographs are highly abnormal and can resemble the respiratory distress syndrome. Acute mortality is as high as 70%. Serology is positive in 80% of cases involving lung disease. Isolation or morphologic identification of the organism from sputum readily confirms the diagnosis. The mainstay of therapy for diffuse pulmonary disease remains amphotericin B, but fluconazole may be preferred in cases of focal pulmonary disease or because of its excellent penetration into the cerebrospinal fluid during meningitis.

Blastomycosis is a rare complication of HIV disease even in areas endemic to *B. dermatitidis*. It can, however, cause a spectrum of pulmonary disease from hilar adenopathy to necrotizing cavitary pneumonia, similar to other granulomatous pulmonary infections.

Aspergillosis is an uncommon complication of HIV disease that can present in several forms, including endobronchial plaques and fulminant parenchymal invasion. Most AIDS patients with aspergillosis have CD4 counts below 50 cells/μL, conventional risk factors (e.g., corticosteroid use or granulocytopenia), or all of those. The chest radiograph shows bilateral or unilateral infiltrates, nodules, or cavities. The chest CT scan may also show filling defects in the airways caused by endobronchial disease. Approximately 50% of patients will respond to amphotericin B, but relapse is common and maintenance therapy with either amphotericin B or itraconazole is indicated. Itraconazole has also been used with some success in initial therapy. Unfortunately, patients with pulmonary involvement generally live less than 6 months after diagnosis.

Kaposi's sarcoma is the most common HIV-related malignancy to involve the lungs. It has recently been found to be caused by infection with human herpes virus 8 and almost exclusively affects homosexual men. Approximately 90% of patients with pulmonary involvement have evidence of mucocutaneous disease on physical examination. The disease may be an incidental finding on chest radiograph or can present with insidious development of dyspnea or cough. Fever is commonly seen, although this is often caused by concomitant infection. The chest radiograph generally shows perihilar, nonspecific patchy infiltrates that may have a reticulonodular pattern. Kerley B lines and pleural effusions are seen in at least 50% of patients. Bulky adenopathy is uncommon. CT scans often show a nodular pattern, with involvement of the bronchovascular bundle in a pattern that fans out from the hilum. The diagnosis is generally made during bronchoscopy by observation of characteristic reddish flat or raised lesions involving the bronchial mucosa. Endobronchial biopsy is generally not performed, because the amount of tissue typically obtained is too small to be diagnostic. (Although the tumor is highly vascular, concerns regarding bleeding after bronchoscopic biopsies have not been borne out.) In the rare case of parenchymal KS without endobronchial disease, transbronchial biopsy has a low yield and open lung biopsy may be needed. Pleural fluid cytology is not helpful because of the nonspecific appearance of the individual sarcoma cells. Likewise, percutaneous pleural biopsy is not helpful because the tumor only involves the visceral pleura. Treatment of pulmonary KS can include chemotherapy, whole lung irradiation, or both, but prolonged control is rare. Interestingly, spontaneous regression has been seen in some patients receiving HAART.

Patients infected with HIV are also at risk for pulmonary involvement with other malignancies. Some case series have suggested that HIV-infected patients are at increased risk for bronchogenic carcinoma and that they develop it at a younger age and with less exposure to tobacco than do noninfected individuals. Patients infected with HIV are also at high risk of developing B-cell lymphoma, in which pulmonary involvement is common and chest radiographs typically disclose multiple nodules or diffuse interstitial infiltrates. Pleural effusions are also common. Primary pulmonary lymphoma, presenting as a solitary mass, occurs less commonly. HIV-related lymphomas are quite aggressive and the median survival after diagnosis is less than 6 months.

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Combination retroviral therapy initiated during treatment for tuberculosis induced temporary worsening of signs and symptoms in one third of patients, although usually not severe enough to warrant discontinuation of therapy. The phenomenon was associated with the return of a positive purified protein derivative (PPD) skin test and likely represented enhanced immune response to infection with TB.

22. Sattler FR, et al. Comparison of trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate-severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS. *J Infect Dis* 1994;170:165.

Trimethoprim-sulfamethoxazole therapy was superior to trimetrexate with leucovorin for patients presenting with $P(A\text{-}a)O_2$ greater than 30 mmHg, although trimetrexate was better tolerated.

23. Schneider MME, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;327:1836.

Of patients on monthly aerosolized pentamidine and patients on once or twice daily TMP–SMX 11% and 0, respectively, developed first-episode Pneumocystis *pneumonia.*

24. Selwyn PA, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS* 1998;12:8858.

At admission, simple clinical variables differentiate TB, PCP, and bacterial pneumonia.

25. Shafer RW, et al. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine* (Baltimore) 1991;70:384.

Diagnosis was often delayed because of decreased PPD reactivity and usually negative sputum smears (despite 90% of sputums eventually growing MTB). Aspirates of lymph nodes, bone marrow, and the liver had the highest immediate yield.

26. Staikowsky F, et al. Mechanical ventilation for *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome: is the prognosis really improved? *Chest* 1993;104:756.

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27. Toma E, et al. Clindamycin/primaquine versus trimethoprim-sulfamethoxazole as primary therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized, double-blind pilot trial. *Clin Infect Dis* 1993;17:178.

Combination clindamycin-primaquine compared with TMP–SMX as primary treatment for mild to moderately severe PCP. Efficacy of both regimens was equal with no significant difference in toxicity, survival, or rate of relapse.

28. Weverling GJ, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. *Lancet* 1999;353:1293.

During 247 person years of follow-up after discontinuation of prophylaxis at median CD4 count of 270, no cases of PCP developed. Almost all had been receiving primary prophylaxis.

29. Wheat LJ, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine* (Baltimore) 1990;69:361.

Systemic syndrome usually dominated, but organism could be grown from the lungs of two thirds of patients. When pulmonary syndrome is prominent, illness is very reminiscent of PCP.

45. HOSPITAL-ACQUIRED PNEUMONIA

Kim M. Kerr

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring 48 hours or later following hospital admission. The definition excludes pulmonary infection that may be incubating at the time of admission. Pneumonia is the second most common hospital-acquired infection, carrying the highest mortality rate of all nosocomial diseases. Between five and ten cases of HAP occur per 1000 hospital admissions, but the incidence is six to twenty times higher in patients receiving mechanical ventilation. In patients who are mechanically ventilated, the development of pneumonia (ventilator-associated pneumonia, VAP) is associated with significant morbidity and higher mortality and substantially increases the cost of patient care.

In the immunocompetent host, HAP can be divided into early and late onset infections. Early pneumonia occurs during the first 4 days of hospitalization, and is often secondary to community-acquired pathogens such as *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, and *Haemophilus influenzae*. Specific risk factors can alter likely pathogens. For instance, if a patient has a witnessed aspiration, anaerobes, enteric gram-negative bacilli, and *S. aureus* should be considered. Recent thoracoabdominal surgery or the presence of an obstructing foreign body are additional risk factors for anaerobic pneumonias. Patients with coma, head injury, recent influenza, recent intravenous drug use, diabetes mellitus, or chronic renal failure are at increased risk for *S. aureus* pneumonias. Corticosteroids predispose patients to pneumonias from fungi, *P. aeruginosa*, and, in some regions of the country, *Legionella* species.

Late onset HAP, occurring 4 days or more after admission, is more commonly caused by *Enterobacter* species, *S. aureus*, *Pseudomonas aeruginosa*, or *Acinetobacter* species. Resistant organisms such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, and *Acinetobacter baumannii* tend to emerge following prolonged mechanical ventilation (>7 days), prior antibiotic use, and the use of broad-spectrum antibiotics (third-generation cephalosporin, fluoroquinolone, or imipenem).

Understanding the pathogenesis of HAP may help in developing mechanisms of prevention. In the normal nonsmoking host, the upper respiratory tract is colonized with aerobic and anaerobic bacteria, whereas the respiratory tract below the vocal cords is sterile. Changes in host defenses can lead to inoculation of the lower respiratory tract with potentially pathogenic bacteria. Colonization and potentially fatal infection can follow inoculation.

Although pathogens can gain access to the lung via inhalation, hematogenous seeding, and contiguous spread, aspiration is the major route of bacterial access in patients with and without endotracheal tubes. Organisms such as *P. aeruginosa* can be inoculated directly into the endotracheal tube of intubated patients, whereas *Enterbacteriaceae* usually colonize the oropharynx before the trachea.

Mechanical ventilation almost always requires the presence of an artificial airway (endotracheal tube or tracheostomy tube). However, the presence of such an airway reduces the effectiveness of the cough reflex, compromises mucociliary clearance, can cause direct injury to the tracheal epithelial surface, and provides a direct pathway for pathogens from the intensive care unit (ICU) environment to the lower respiratory tract. A *biofilm* of bacteria-laden accretions on the luminal surface of the endotracheal tube, with subsequent dislodgement into the lower airways, can also contribute to the development of VAP. Novel solutions to the biofilm problem include the development of less-adhesive polymers to prevent material accumulation in the lumen of the tube or a new double layer endotracheal tube with a disposable cannula. Aspiration around the cuff of the endotracheal tube is another mechanism by which bacteria can access the lower respiratory tract. To reduce the amount of secretions pooling on top of the endotracheal tube cuff, a specific endotracheal tube (HI-LO EVAC tube, Mallinckrodt, St. Louis, Missouri) was designed with a separate lumen that allows removal of secretions from the subglottic space above the tube. Two randomized trials showed a 50% reduction in the incidence of VAP with the use of this technique. Problems with the use of this device are the additional cost and the need to have these endotracheal tubes available when patients undergo tracheal intubation (emergency room, operating room, ICU, wards).

Nasogastric feeding tubes (NGT) have been implicated as a risk factor for pneumonia, presumably because of an increased incidence of gastroesophageal reflux or aspiration. The supine head position has also been linked to an increased incidence of aspiration and bacterial colonization of the lower airways in ventilated patients and is a risk factor for the development of VAP. Clinical data suggest that the simple maneuver of elevating the head of the bed, especially for patients with feeding tubes, may be a safe and inexpensive means of lowering the incidence of VAP. In addition, efforts aimed at preventing gastric over-distension may also decrease the risk of aspiration and VAP; however, no large prospective trials have yet been performed to support this preventive measure.

The role that gastric colonization plays in VAP is a controversial issue that has generated multiple clinical trials with conflicting results. At the center of the controversy is the relationship between VAP, gastric colonization, and stress ulcer prophylaxis. The acidic environment of the gastric lumen prevents bacterial growth under normal physiologic circumstances. However, gastric acidity can be reduced by critical illness or advanced age, or with the administration of antacids or H_2 antagonists. The cytoprotective agent sucralfate has been claimed to prevent stress ulcers without altering gastric acidity. Several studies have shown the use of sucralfate to be associated with a lower incidence of VAP when compared with antacids or H_2 antagonists. However, the methodologies of these studies have been criticized, and other studies have yielded conflicting results. Given its relatively low cost and safe pharmacologic profile, sucralfate is an appealing method of providing stress-related upper gastrointestinal bleeding prophylaxis in critically ill patients at high risk (e.g., those with coagulopathy, respiratory failure, severe burns, head trauma, or multiple trauma). However, the optimal agent that minimizes the risk of both stress ulcers and VAP has yet to be determined.

Although the role of gastric colonization in VAP is uncertain, convincing evidence indicates colonization of the oropharynx often precedes colonization of the trachea and subsequent development of VAP. Selective decontamination of the digestive tract (SDD) is a strategy designed to prevent oropharyngeal and gastric colonization with aerobic gram-negative bacilli and *Candida* species without altering the anaerobic flora of the gut. Some proposed regimens use a combination of nonabsorbable antibiotics applied as a paste to the oropharynx or given via the NGT, whereas others also include a systemic antibiotic such as intravenous cefotaxime. Although several clinical trials have demonstrated a decrease in the rates of lower respiratory tract infections with SDD, others have found no difference in the incidence of VAP. Most studies have not been able to demonstrate a reduction in mortality rate, duration of stay, or hospital costs with the

use of SDD. In addition, concerns exist about the emergence of antibiotic-resistant organisms with these regimens. Therefore, the routine use of SDD to prevent VAP is not recommended at present.

The diagnosis of HAP, and in particular VAP, has been the subject of numerous studies and heated debates. It is generally accepted that relying solely on clinical criteria (e.g., fever, leukocytosis, purulent tracheal secretions, and a new or progressive infiltrate on chest radiographs) can often be misleading. What has yet to be agreed on is the role of blind and bronchoscopically guided culture techniques in the diagnosis of VAP. At issue for all microbiologic techniques are (a) the accuracy and reproducibility of the collection methods used; (b) the appropriate bacteriologic thresholds to define pneumonia; (c) the costs and risks associated with each procedure; and (d) the effect of the techniques on overall clinical outcomes. One problem in assessing the various diagnostic maneuvers is that no true *gold standard* exists for accuracy with which to compare diagnostic techniques such as quantitative tracheal aspirates, quantitative bronchoalveolar lavage (BAL), or protected brush specimens. Even when open lung biopsy has been performed, significant interobserver variability has been noted between pathologists when making the diagnosis of pneumonia based on histologic criteria.

Because of the significant questions regarding the sensitivity, specificity, and reproducibility of invasive diagnostic techniques for the diagnosis of HAP, a conservative approach seems warranted. When nosocomial pneumonia is suspected, a sputum or tracheal aspirate specimen should be obtained for Gram's stain and culture. The Gram's stain allows for the evaluation of the quality of the respiratory sample. Finding more than 10 squamous epithelial cells per low-powered field in an expectorated sputum specimen suggests oropharyngeal contamination; culture results will likely be unreliable. In addition, if the sample demonstrates fewer than 10 neutrophils per low-powered field, a diagnosis other than pneumonia should be suggested. However, the absence of neutrophils does not conclusively exclude an infectious process, because factors such as sampling errors and leukopenia can make this finding misleading. In the intubated patient, contamination of oropharyngeal specimens is less of a concern, but colonization of the endotracheal tube lumen itself can confound the interpretation of microbiologic studies. Cultures of tracheal aspirates are very sensitive for detecting the organism responsible for the pneumonia, but are not very specific. Differentiating organisms that are colonizers from true pathogens is extremely difficult. Semiquantitative cultures can provide information regarding the relative number of pathogens in the specimen, but not necessarily distinguish between colonizing and infecting bacteria. In addition, semiquantitative cultures are not available at all institutions and many patients who develop HAP are already on antibiotics that may alter the results of this technique. Blood cultures should be obtained in the evaluation of suspected HAP, as should pleural fluid analysis in patients with pleural effusion. Isolation of organisms from these normally sterile fluids is diagnostic.

Treatment of nosocomial pneumonia should be initiated promptly and not await the results of microbiologic tests. Early use of appropriate antibiotic therapy, before obtaining culture results, appears to have the greatest likelihood of improving patient outcome. The American Thoracic Society recently published recommendations that, along with local (hospital/ICU) resistance patterns, may help in selecting appropriate antibiotics for empiric treatment of HAP. Consideration to previous antibiotics the patient may have received is also necessary when selecting empiric coverage for HAP. Inadequate initial empiric antibiotic therapy most frequently results from omission of treatment for MRSA or gram-negative bacteria with resistance to previously used antibiotics (*P. aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, and *Enterobacter* species) and is associated with a high mortality.

Of particular relevance to the choice of empiric antibiotic regimens for HAP are (a) the presence or absence of underlying medical conditions; (b) when, during the hospital course, the patient developed HAP (early < 4 days, or late > 4 days); and (c) the presence of specific risk factors for infection with particular organisms. Previously healthy patients who develop early onset HAP can usually be treated with a second-generation cephalosporin, a *nonpseudomonal* third-generation cephalosporin, or a combination β-lactam/β-lactamase inhibitor. Those who develop late onset HAP or

are critically ill or have recently been on antibiotics should receive broader antibiotic coverage to include resistant and virulent organisms such as *P. aeruginosa*, *Acinetobacter* and *Enterobacter* species, and MRSA. Empiric therapy in these circumstances commonly includes two synergistic antipseudomonal agents as well as vancomycin. Hospital-acquired *Pseudomonas* infections almost always occur in patients who have previously received antibiotics, so reuse of the same class of antibiotics should be avoided in selecting initial empiric therapy. The spectrum of antibiotic coverage can frequently be narrowed 2 to 3 days into the treatment course, based on culture and sensitivity results as well as on the patient's response. Tailoring of antibiotic treatment as soon as possible is important to minimize the development of resistant organisms and to avoid the cost and adverse effects of unnecessary medications. Treatment of specific organisms is addressed elsewhere in this book. The duration of therapy is usually 7 to 21 days, based on the severity of illness, the infecting pathogen, and the rapidity of clinical response.

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Delay of adequate therapy until bronchoscopy is performed or until BAL results are known results in increased mortality in patients with suspected VAP.

IV. AIRWAYS DISEASE

46. ASTHMA: CLINICAL PRESENTATION AND DIAGNOSIS

Timothy D. Bigby

No definition of asthma is universally accepted. Clinicians have long recognized that asthma is characterized by reversible airway obstruction in association with dyspnea, cough, and sputum production. Attempts to define asthma in pathophysiologic terms now include the physiologic finding of airway hyperresponsiveness and the pathologic finding of airway inflammation.

Asthma is a common disorder in the United States, affecting approximately 15 million people including 5 million children. It is the most common chronic disease of children. It is more common in urban than rural populations; the incidence is higher among minority populations. Although one half of patients develop asthma before their tenth birthday, the disease can develop at any age. At least one half of children who develop asthma will have remission as adults, but adult-onset asthma rarely abates. The prevalence, severity, and mortality rate associated with asthma clearly has increased over the last 40 years. The explanation is unclear, but urban living conditions, exposure to oxidant pollutants, passive smoking, and even current therapies have been implicated. More recent concerns have been raised about relationships to the modernization of western culture, including a decreased incidence of common childhood infectious diseases, widespread antibiotic use, declining physical fitness in children, and rising incidence of obesity beginning in childhood.

Our knowledge of the airway pathology associated with asthma has expanded, but the basic observations are unchanged. The airways of asthmatics are characterized by mixed inflammatory cell infiltration; eosinophils are the most striking feature, but these infiltrates also include large numbers of less easily recognized mast cells, neutrophils, lymphocytes, and macrophages. The inflammatory changes are also associated with denudation of airway epithelium and mucous gland hypertrophy. Long-standing asthma can be associated with subepithelial fibrosis and smooth muscle hypertrophy. Currently, substantial interest is seen in this *remodeling* of the airway, its long-term consequences, and potential treatments.

The cause of asthma remains essentially unknown. An older hypothesis suggested that so-called *intrinsic asthma* (i.e., asthma in individuals without identifiable triggers) might be neurally mediated. However, a distinct abnormality of the sympathetic or parasympathetic nervous systems has not been found in asthmatics. Mutations of the β_2 adrenergic receptor have now been described, although the significance of these mutations is still under investigation. Newer studies of muscarinic receptors suggest that these may play a role. The peptidergic nervous system is also an active investigative interest. Substantial data support an allergic pathogenesis mediated predominantly by both inhaled and systemic antigens. Allergy appears to play a central role in sustained wheezing in early childhood that can be characterized clinically as asthma; some studies suggest that most asthma begins in childhood. Cytokines released by Th2 lymphocytes are increasingly recognized as important in allergic and, possibly, all asthma.

During the last two decades, an association between airway hyperresponsiveness and inflammation in asthma has been noted. Multiple studies have demonstrated that airway inflammation precedes the development of hyperresponsiveness. In some models, if this inflammatory cell influx is blocked, hyperresponsiveness does not develop. Thus, most investigators now believe that, despite multiple triggers for the inflammatory cell influx, airway inflammation is the common pathway by which airway hyperresponsiveness is induced. These inflammatory cells also appear to be the source of mediators that induce acute bronchoconstriction, mucus hypersecretion, airway edema, and further inflammatory cell influx. However, the inflammatory milieu is complex and a single inflammatory cell or inflammatory mediator is unlikely to explain all of the clinical features of asthma. Although a genetic component of asthma clearly exists, it

is not explained by a single gene, but instead is a complex genetic disorder. Thus, asthma is polygenic and the phenotypic expression of involved genes is significantly influenced by environmental factors. A variety of candidate genes in asthma are currently under investigation.

Intermittent reversible airway obstruction, hyperresponsiveness, and inflammation characterize the asthma phenotype. The clinical hallmarks are well known: episodic wheezing with dyspnea, cough, and sputum production. Between acute episodes, symptoms improve or can fully remit. These symptoms can vary from mild to severe, with profound limitation of activity and symptoms at rest. Patients often do not notice symptoms of obstruction until their acute exacerbation is of moderate to severe intensity. A detailed history of factors that precipitate acute symptoms is critical in subsequent management.

The 1997 National Asthma Education and Prevention Program, Expert Panel Report II provides a relatively simple classification of chronic asthma that has direct implications for treatment. This report stratifies severity of disease into *steps* of severity that can be used to determine appropriate therapy (a *step-care* approach). These guidelines have been well received by pulmonary and allergy clinicians. The stratification includes mild intermittent (step 1), mild persistent (step 2), moderate persistent (step 3), and severe persistent disease (step 4) (Table 46.1). Patients with mild intermittent asthma have only occasional symptoms (two or fewer times per week), normal pulmonary func-

Table 46.1. Classification of asthma severity

	Symptoms	Nighttime Symptoms	Lung Function
Step 4: Severe persistent	• Continual symptoms • Limited physical activity • Frequent exacerbations	Frequent	• $FEV_1/PEF \leq 60\%$ predicted • PEF variability > 30%
Step 3: Moderate persistent	• Daily symptoms • Daily use of inhaled short-acting β_2-agonist • Exacerbations ≥ 2 times a week; may last days	> 1 time a week	• $FEV_1/PEF > 60\%$ to < 80% predicted • PEF variability > 30%
Step 2: Mild persistent	• Symptoms > 2 times a week but < 1 time a day • Exacerbations may affect activity	> 2 times a month	• $FEV_1/PEF \geq 80\%$ predicted • PEF variability 20% to 30%
Step 1: Mild intermittent	• Symptoms ≤ 2 times per week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days); intensity may vary	≤ 2 times per month	• $FEV_1/PEF \geq 80\%$ predicted • PEF variability < 20%

PEF, peak expiratory flow.

Modified from National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. NIH publication No. 97–4051, 1997.

tion, modest variability in peak expiratory flow (PEF), and use intermittent inhaled β_2 agonists no more than two times per week. Patients with mild persistent asthma have symptoms more than twice per week but less than once per day, normal pulmonary function between exacerbations, and more significant variability in PEF with exacerbations. Patients with moderate persistent asthma have daily symptoms that interfere with activity, require daily use of a β_2 agonist for quick relief, and have abnormal baseline pulmonary function with more severe variability of PEF. Patients with severe persistent asthma have continuous symptoms that significantly impair their activities, limited physical activity, frequent exacerbations, and more abnormal baseline pulmonary function with more dramatic variability of PEF.

Historical details, such as the age of onset, frequency and severity of episodes, requirements for medications, hospitalizations, and prior need for mechanical ventilation, are important to document. Daily fluctuations in symptoms are also important. Some patients have predominantly nocturnal symptoms; these symptoms can be associated with uncontrolled reflux esophagitis, sinusitis, or pharyngeal dysfunction. Daily fluctuations can also be precipitated by exertion or exposure to a variety of environmental agents including cold, dry air, oxidant pollutants, tobacco smoke, perfumes, dust, or provocative agents in the workplace. Symptoms that increase throughout the workday or workweek and tend to improve with days off from work suggest the possibility of occupational asthma. A history of allergy, atopy, eczema, allergic rhinitis, or nasal polyps may be elicited. Medication allergies or symptoms associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can also be associated with asthma. The syndrome of sensitivity to NSAIDs, nasal polyps, and asthma has been termed *triad asthma* or Samter's syndrome. Patients with asthma should be instructed to avoid these drugs and patients with sensitivity to them should be advised to strictly avoid them.

Cough occasionally is the only symptom of asthma; in the evaluation of chronic cough, asthma should be included in the differential diagnosis. The cough associated with asthma can be dry, but it is often productive of thick, tenacious sputum, which may contain mucous plugs. The sputum may become purulent as symptoms worsen. This may represent secondary bacterial infection but more often is caused by inflammatory cell infiltration without viral or bacterial superinfection. This purulent sputum most often contains numerous eosinophils.

Physical findings in asthma correlate poorly with more objective measures of airway obstruction, such as pulmonary function tests. Nevertheless, the findings are clinically useful. In an asymptomatic asthmatic patient, physical findings may be absent; however, wheezing may be elicited by forced expiration. Mild bronchospasm, in general, is associated with wheezing only during expiration. With greater degrees of obstruction, wheezing is heard in both the inspiratory and expiratory phases, with prolongation of the expiratory phase. With profound obstruction, wheezes may be heard only during the inspiratory phase or may even be absent with profoundly diminished air movement. When wheezing is correlated with other physical examination findings, a more reliable assessment can be made of the severity of obstruction. Normally the inspiratory-to-expiratory ratio is less than 1:2, but this ratio increases in a graded fashion to 1:3 or more with increasing degrees of airway obstruction. With severe obstruction, the intensity of breath sounds diminishes. Patients also begin to utilize accessory muscles of respiration with moderate to severe acute bronchospasm and may have active rather than passive expiration. With significant obstruction, evidence may also be seen of hyperinflation with low diaphragms and an increased anteroposterior diameter. The degree of obstruction correlates crudely with pulsus paradoxus. A pulsus greater than 10 mmHg is abnormal, and greater than 20 mmHg suggests profound obstruction. However, this measure should not substitute for direct measures of the degree of obstruction by PEF measurements or measurement of forced expiratory volume in 1 second (FEV_1). With severely labored respirations, the patient can become diaphoretic, anxious, and unable to speak in full sentences. A respiratory rate greater than 30 breaths per minute and a heart rate of 120 beats per minute suggest severe bronchospasm. Agitation, confusion, somnolence, and cyanosis are foreboding findings and suggest impending respiratory failure. Unilateral loss of breath sounds can be consistent with mucous plugging and secondary atelectasis, but these findings also must raise the possibility of pneumothorax.

The clinical laboratory examination of asthmatics is often of limited value. Peripheral blood eosinophilia is frequently present but rarely exceeds 25%. Serum IgE is often elevated in asthmatics, and in allergic asthmatics, specific antibodies can be detected. Very high serum IgE should raise the question of allergic bronchopulmonary aspergillosis. Likewise, examination of sputum or nasal mucus can often reveal the presence of increased numbers of eosinophils. None of these laboratory tests is specific for asthma or significantly alters management in most patients.

During bronchospasm, spirometry reveals obstruction with a decrease in FEV_1 and decreased midexpiratory flows. The FEV_1 to forced vital capacity (FVC) ratio is also reduced. With more severe obstruction, hyperinflation is evident, with an increased residual volume and functional residual capacity more than total lung capacity. The flow-volume loop reveals evidence of obstruction with diminished flows and caving inward of the expiratory limb. One of the hallmarks of asthma is partial or complete reversal of airway obstruction after the administration of a bronchodilator. This response can also be used to gauge the adequacy of treatment. However, the lack of response to a one-time dose of bronchodilator does not preclude a reversible component to the patient's obstruction. Moreover, we now recognize that asthma is associated with a progressive decline in lung function over years; presumably, this decline is caused by fixed airway obstruction associated with airway remodeling. The diffusing capacity of the lung for carbon monoxide is often increased in asthmatics who do not smoke. The exact mechanism of this increase is unknown, but it is thought to represent an increase in pulmonary capillary blood volume associated with obstruction. Peak expiratory flow measurements, which are inexpensive, simple measurements that patients can assess and interpret, are also reduced during bronchospasm.

Bronchial challenge testing can be used to establish the presence of airway hyperresponsiveness. Nonspecific bronchial hyperresponsiveness is demonstrated by exaggerated bronchoconstriction to inhaled histamine or methacholine. Nonspecific bronchial challenge is most useful in the evaluation of cough or to establish the diagnosis of asthma when the history is compatible but physical examination and pulmonary function evidence of obstruction are lacking. However, bronchial challenge can be hazardous and should not be performed when significant airway obstruction is present. Bronchial challenge with specific provocative agents has utility in selected cases. The most commonly used specific bronchial challenges are exercise or cold air. Specific airway challenges with other agents (e.g., antigen) should only be performed in specialized centers having experience with these procedures.

Assessment of arterial blood gases is usually not necessary in the management of mild to moderate asthma. However, pulse oximetry may be of value during moderately severe exacerbations and arterial blood gases may be indicated during severe exacerbations. Hypoxemia is a frequent finding in this setting, and the arterial P_{CO_2} is usually decreased. During prolonged and severe episodes of airway obstruction, the patient can develop respiratory muscle fatigue, and the P_{CO_2} may normalize or become elevated. A normal or elevated P_{CO_2} during a severe exacerbation is an ominous sign, suggesting impending respiratory failure.

In the setting of chronic asthma and in the absence of another underlying condition, chest radiographic findings are usually normal. During an exacerbation, chest radiographs are not required unless fever, sputum production, chest pain, leukocytosis, or physical evidence of barotrauma are present. Hyperinflation of the lung can be present during severe exacerbations.

The diagnosis of asthma is made principally on clinical grounds; laboratory data are used in a supplementary or confirmatory fashion. A history of episodic wheezing in a nonsmoking patient, with findings of wheezing on physical examination, is strongly suggestive of asthma. Other causes of wheezing should be excluded. The diagnosis is confirmed with spirometry, which demonstrates obstruction (a FEV_1 of 80% of predicted or less with a reduced FEV_1:FVC ratio) that normalizes or significantly improves with use of a bronchodilator. If spirometry is normal, it should be repeated after a forced expiratory maneuver, which usually induces a fall in FEV_1 in asthmatics. If spirometry still remains normal, consider bronchial challenge testing. Alternatively, the patient can be followed over time with serial spirograms (or PEF monitoring) to demonstrate variable obstruction.

Not all patients who wheeze have asthma. Additional diagnoses should be considered in both the acute and chronic settings. Upper airway obstruction, tracheomalacia, and tracheal or bronchial masses can all masquerade as asthma. These disorders are usually distinguished by the presence of stridor or focal wheezing on physical examination with flow limitation on a flow-volume loop. Laryngeal (vocal cord) dysfunction can be clinically indistinguishable from asthma. This disorder is caused by inappropriate apposition of the vocal cords during the respiratory cycle, which can be successfully treated by speech therapy. Laryngeal dysfunctions are often misdiagnosed and, when severe, can be treated with systemic corticosteroids for presumed severe asthma. Flow-volume loops demonstrate normal or near normal expiratory flow with a flow-limited inspiratory limb. Vocal cord dysfunction is confirmed by direct laryngoscopy.

Patients with chronic fixed airway obstruction (e.g., emphysema or chronic bronchitis) can have acute wheezing episodes, most often associated with exacerbations of their disease. These patients often have airway hyperresponsiveness that is enhanced during their exacerbation. Previously, these patients have been labeled as having *asthmatic bronchitis*. A history of smoking, poor response to aggressive bronchodilator therapy, and spirometric findings of obstruction that do not reverse over time differentiate them from asthmatics. Acute bronchitis can also be associated with the development of airway hyperresponsiveness, most commonly after a viral respiratory tract infection. Most patients have transient symptoms that resolve spontaneously, but a small subgroup may develop sustained clinical asthma. Similarly, other respiratory tract infections are associated with wheezing, and some patients may develop sustained asthma. Left ventricular failure, pulmonary embolus, hypersensitivity pneumonitis, sarcoidosis, lymphangiomyomatosis, and pulmonary helminth infections should also be considered. Eosinophilic vasculitis (Churg-Strauss syndrome) can also masquerade as asthma with the symptoms or signs of vasculitis masked by the use of corticosteroids.

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47. ASTHMA: MANAGEMENT

Shazia M. Jamil and Timothy D. Bigby

The management of asthma continues to evolve, reflecting a clearer view of pathophysiology and the role of inflammation. In 1997, the classification of asthma severity was modified to include the categories of (1) mild intermittent; (2) mild persistent; (3) moderate persistent; and (4) severe persistent. These categories more accurately correlate with clinical manifestations. New medications include leukotriene modifiers (including cysteinyl leukotriene receptor antagonists and 5-lipoxygenase inhibitors), longer acting β_2-agonists, potent inhaled corticosteroids, and nedocromil. The primary goal of asthma therapy is still to allow the patient to maintain a normal or near-normal lifestyle by (1) preventing chronic and recurrent symptoms; (2) maintaining normal to near-normal pulmonary function; and (3) providing optimal pharmacotherapy.

Patient education is the most important nonpharmacologic intervention. A comprehensive understanding of the disease and its treatment allows the patient to participate actively in the care program, recognize potential problems, obtain early treatment, and avoid exacerbations that might lead to hospitalization. The correct use of metered-dose inhalers (MDIs) and the value of spacers should be emphasized. Inexpensive and portable peak flow meters are recommended, particularly for patients with moderate to severe persistent asthma. Daily monitoring of peak expiratory flow (PEF), a simple, quantitative, and reproducible index of airflow obstruction, can detect early changes in airway function and disease status. Spirometry is indicated at baseline and after stabilization to document a patient's *personal best* function. Spirometry should be repeated every 1 to 2 years to assess airway function. Optimal asthma management is best facilitated by a written action plan describing the steps a patient should take based on symptoms and PEF.

Successful long-term management of asthma can be challenging. It is essential to identify and reduce exposure to inhaled allergens, occupational precipitants, and irritants. The patient should be asked about exposure to pets, house-dust mites, cockroaches, indoor molds, and outdoor allergens. Patients with an allergic component should avoid, or at least reduce, such exposure. Patients with persistent asthma with an inconclusive allergic history may undergo skin testing. If a clear relationship between an allergen and symptoms is detected, immunotherapy may be considered. All asthmatics should abstain from smoking and avoid exposure to second-hand smoke. Patients with severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs should avoid these agents as fatal exacerbations have been reported. Patients should also avoid nonselective β-blockers, including topical ophthalmologic preparations, as they can cause exacerbations of asthma. Patients with persistent asthma should receive yearly influenza vaccine. Pneumococcal vaccine is no longer recommended for asthmatics. Careful evaluation and treatment of concomitant conditions (e.g., chronic rhinitis, chronic sinusitis, vocal cord dysfunction, and gastroesophageal reflux disease) may alleviate particularly difficult-to-control asthmatic symptoms.

Asthma medications are classified as *quick-relief* (rescue) and *long-term* (control) medications. Quick-relief medications, taken to promptly reverse airflow obstruction and relieve symptoms, include short-acting β_2-agonists, anticholinergics, and systemic corticosteroids (the earliest effect of corticosteroids is the upregulation of β_2-receptors within 8 hours). Long-term medications, taken daily to maintain control of persistent asthma, include corticosteroids, leukotriene modifiers, long-acting β_2-agonists, theophylline, nedocromil, and cromolyn.

The mainstay of pharmacologic therapy for mild intermittent asthma is inhaled, short-acting β_2-agonists, as needed for symptoms. Patients whose asthma is not adequately controlled with this medication alone are considered to have persistent disease. Mild persistent asthma is defined, in part, as asthma requiring inhaled β_2-agonists more than twice per week for relief of symptoms (*National Asthma Education and Prevention Program Guidelines*). Patients with persistent disease require the long-term control medication in addition to a short-acting β_2-agonist on an as-needed basis.

Inflammation plays a key role in asthma and anti-inflammatory medications are most effective for long-term control. However, the distinction between drugs with or without anti-inflammatory properties has become progressively vague as more anti-inflammatory properties have been discovered for medications that traditionally have not been considered to be anti-inflammatory.

For patients with mild persistent asthma, the control agent of choice is low-dose inhaled corticosteroids (equivalent to 8–10 puffs of beclomethasone per day). High-dose inhaled corticosteroids (equivalent to 16–20 puffs of beclomethasone per day) have not proved to be superior to the low-dose regimen. This is particularly important in light of recent data suggesting that inhaled corticosteroids may have clinically relevant long-term side effects. The use of a spacer with mouth rinsing after inhalation decreases local side effects and systemic absorption. A dose-dependent reduction in bone mineral content probably occurs with long-term inhaled corticosteroids. For this reason, physicians should consider calcium (1000–1500 mg daily) and vitamin D (400 IU daily) supplements for older postmenopausal women. For patients who cannot or will not take inhaled corticosteroids, alternatives can include long-acting β_2-agonists, leukotriene modifiers, the chromones (cromolyn and nedocromil), and theophylline. These agents are less effective than inhaled corticosteroids as first-line control therapy except in specific circumstances (see below).

Patients with moderate persistent asthma should be treated with daily low-dose inhaled corticosteroids in combination with other long-term control therapy that should be tailored to the patient, but can include long-acting β_2-agonists, leukotriene modifiers, a chromone, or theophylline. Several reports have demonstrated that a combination of one of these agents with inhaled corticosteroids is superior to high-dose inhaled corticosteroids alone and may be equivalent to a combination of one of these agents with high-dose inhaled corticosteroids. If symptoms or pulmonary function are not adequately improved with inhaled corticosteroids plus another long-term control agent, additional medications can be added. Daily use of a long-acting β_2-agonist is generally well tolerated, but should not exceed 84 μg (salmeterol; two puffs twice a day) and should not be used on an as-needed basis for acute symptoms. High-dose inhaled corticosteroids should be reserved for those who fail these multiple combinations. The role of anticholinergics in the long-term management of asthma has not been established, although they may be moderately effective for a subset of asthmatics.

Patients with severe persistent asthma typically have symptoms and altered pulmonary function that are not adequately controlled with high-dose inhaled corticosteroids plus other long-term control therapies. These patients require chronic systemic corticosteroids. Because of serious long-term consequences of chronic systemic corticosteroids, every attempt should be made to improve the management of these patients with environmental control, improved combinations of other long-term control medications, and attempts to taper systemic corticosteroids to the lowest dose possible. Patients on chronic oral corticosteroids should be treated no more frequently than once per day, except in rare circumstances; alternate-day therapy is preferred whenever possible. Patients should also be monitored closely for related adverse effects. Occasionally, patients may not have their severe persistent asthma adequately controlled despite daily systemic steroids. After careful re-evaluation and maximal adjustment of medications, these patients may be considered for cytotoxic or immunosuppressive therapy. This should only be considered by a specialist who is experienced in the use of such medications.

Written self-management plans for patients with a good fundamental understanding of their disease are useful both for chronic management and during acute exacerbations. The usual initial plan during an exacerbation is to increase the dose and shorten the interval of inhaled β_2-agonists. Ipratropium bromide used with a short-acting β_2-agonist may provide additional bronchodilation. Purulent sputum in this setting may be caused by inflammatory cell influx rather than infection. Nevertheless, many practitioners use antibiotics empirically with severe exacerbations; sputum cultures to guide therapy are preferred in less severe circumstances. Indiscriminate use of antibiotics should be discouraged. When symptoms do not remit with more aggressive use of inhaled β_2-agonists, early intervention with systemic corticosteroids is pivotal and should always precipitate contact with a physician. A typical schedule would begin with 40 to 60 mg/d of prednisone, tapered over 10 to 14 days. The dosage can be

tapered rapidly and discontinued if the total course is less than 14 days. However, patients with more severe or more frequent exacerbations or those with prior use of corticosteroids may require a more gradual taper to avoid treatment failure and readmission. When the dose of oral corticosteroid has been reduced to approximately 20 mg/d of prednisone, or equivalent, reinstitution of inhaled corticosteroids is appropriate. Usually, inhaled corticosteroids are discontinued during acute exacerbations because of the tendency for some of these preparations to exacerbate bronchospasm via irritant effects. This is most common for inhaled corticosteroids supplied as a suspension rather than a solution. This issue has been re-evaluated in recent years; some inhaled corticosteroids can provide therapeutic benefit during exacerbations. The physiologic abnormalities associated with an acute exacerbation of asthma persist well after symptomatic improvement. Therefore, intensive therapy and close follow-up should be continued for an extended period following the resolution of symptoms.

Status asthmaticus is life-threatening asthma characterized by sustained, severe airway obstruction refractory to treatment. These patients should always seek emergent medical care. Initial treatment should include oxygen, higher and more frequent doses of inhaled β_2-agonists, and early institution of systemic corticosteroids because of the delay in the observed clinical response (i.e., 6–8 hours). Small volume nebulizers, metered dose inhalers (MDIs), and continuous administration by a nebulizer are all effective methods for delivering β_2-agonists; however, numerous studies indicate that a MDI with a spacer is as effective and is more cost-efficient than a nebulizer. Spacers are particularly important when a MDI is used for adults who are unable to coordinate their inspiratory effort with activation of the MDI. β_2-agonists can be administered by the subcutaneous route; however, this results in greater toxicity and has no greater benefit over the aerosol route. A commonly used corticosteroid is methylprednisolone in a dose of approximately 60 mg every 6 hours. These high doses are not benign; potential complications include hypokalemia, hyperglycemia, acute central nervous symptom alterations, hypertension, and peripheral edema. Use of parenteral theophylline in this setting is controversial; many studies have shown no added bronchodilator effect and substantial increases in toxicity. The value of magnesium sulfate in the treatment of status asthmatics has not been studied rigorously; it cannot be used repeatedly but can provide some modest, transient improvement in lung function.

During severe exacerbations, respiratory failure can develop despite maximal therapy. Hypercapnia alone does not necessitate intubation, and can be effectively managed in some cases with noninvasive mechanical ventilation by face mask. The goal is to allow time to optimize pharmacologic management. The presence of peak flows (<150 L/min), pulsus paradoxus (>20 mm Hg), thoracoabdominal paradox, hypoxemia despite oxygen therapy, or an increasing $Paco_2$ signals the potential for progression to respiratory failure requiring intubation and mechanical ventilation.

Hydration should be used to attenuate hypotension that is frequently observed after the institution of positive pressure ventilation. Sodium thiopental, etomidate, narcotics, ketamine, and benzodiazepines have all been used safely for sedation or anesthesia at the time of intubation in the acute asthmatic patient. Muscle relaxation is often required and is usually accomplished with succinylcholine; however, acidemic patients should be monitored carefully because of the potential for hyperkalemia. Concomitant use of non-depolarizing, neuromuscular blocking agents with systemic corticosteroids has been associated with myopathy and severe peripheral muscle weakness; thus, they should be used with caution.

Once the patient is intubated, careful attention to tidal volumes, peak flows, and inspiration to expiration ratios is necessary to minimize barotrauma, which is a significant risk in this setting. To minimize intrinsic positive end-expiratory pressure ($PEEP_i$), the time available for expiration should be maximized by increasing the inspiratory flow rate and reducing the respiratory frequency. It may also be necessary to reduce the tidal volume to increase expiratory time. In turn, permissive hypercapnia in some patients may help to avoid dramatically elevated airway pressures. Intravenous bicarbonate can be used with permissive hypercapnia to partially compensate for the resulting respiratory acidosis, but it must be used judiciously to maintain arterial pH greater than 7.20. Often higher doses of inhaled β_2-agonists and ipratropium bromide are required through in-line MDI treatments at more frequent intervals because of the severity of

bronchospasm and the decreased efficiency of aerosol delivery through the ventilator circuit. Intravenous theophylline is of questionable benefit and can be risky; if used, theophylline drug levels should be monitored closely. Monitoring of peak to plateau airway pressure gradients and auto-PEEP may help in assessing the severity of bronchospasm and response to therapy. These patients should receive an extended course of oral corticosteroids (at least 4–6 weeks) and should not be tapered below 20 mg/d until seen by a physician in follow-up. Some experts argue that patients with a life-threatening episode of asthma requiring mechanical ventilation should be treated with systemic corticosteroids for an extended period (perhaps 1 year) because of the high risk of another episode.

Some specific circumstances warrant special considerations in asthma. Exercise-induced asthma is common, especially in young asthmatics. Symptoms are often controlled by use of short-acting, inhaled β_2-agonists before exercise. For more persistent symptoms, a regularly scheduled long-acting β_2-agonist, a leukotriene modifier, or a chromone should be considered. Similarly, nocturnal asthma can be particularly troubling, often requiring long-acting drugs. With persistent nocturnal symptoms despite inhaled corticosteroids, long-acting β_2-agonists, leukotriene modifiers, or theophylline should be considered. Patients with aspirin-sensitive asthma usually have moderate to severe symptoms which can be difficult to control. Leukotrienes are thought to play a particularly important role; thus, leukotriene modifiers should be strongly considered in these patients.

Asthma is the most common potentially serious medical condition complicating pregnancy. Uncontrolled asthma during pregnancy can produce complications in both the mother and the fetus. A recent report by the Working Group on Asthma and Pregnancy found that undertreatment, principally attributable to unfounded fears of fetal affects of medication, is the major problem in asthma management during pregnancy. The greatest experience in the pregnant patient is with inhaled β_2-agonists and theophylline; however, corticosteroids, cromolyn, and anticholinergics have all been used safely. Thus, asthma should be treated as aggressively in pregnant as in nonpregnant women. Special emphasis should also be placed on nonpharmacologic measures to avoid asthma triggers. Asthma care should include monitoring of fetal growth, maternal symptoms, and maternal lung function. All pregnant asthmatics should be tested with spirometry; the single best index of severity is the forced expiratory volume in 1 second (FEV_1), which is not significantly altered by pregnancy. Patients with moderate or severe asthma should be monitored with twice daily measurements of peak expiratory flow rate and should report the values to the physician at each prenatal visit. After the first trimester, patients should receive influenza vaccine.

The basic management of asthma during pregnancy is very similar to that in nonpregnant patients and is based on asthma severity classification. If the patient's asthma is more than mild intermittent, anti-inflammatory therapy is recommended. Cromolyn sodium is a reasonable first choice; however, if inhaled corticosteroids are used, beclomethasone is preferred. The immediate goals of therapy of severe asthma exacerbation in pregnancy are to correct hypoxemia, alleviate bronchospasm, avoid maternal exhaustion or respiratory failure, and prevent fetal morbidity and mortality. The management of acute exacerbation includes oxygen to maintain a minimum Pao_2 (>60 mm Hg) (oxygen saturation > 95%), inhaled β_2-agonist, and a short course of systemic corticosteroids. During labor and delivery, patients who have required long-term systemic corticosteroids should be given hydrocortisone because of the risk of maternal adrenal suppression.

Asthmatics are at risk for respiratory complications during and after surgery, including acute bronchospasm triggered by intubation and hypoxemia. Therefore, patients with asthma should be evaluated before surgery, including a review of symptoms and medications, measurement of pulmonary function, and attempts made to optimize lung function. A short course of corticosteroids may be necessary. It is recommended that patients who have received systemic corticosteroids for more than 2 weeks during the past 6 months, be given hydrocortisone (100 mg every 8 hours) intravenously on the day of surgery, with a rapid reduction of the dose within 24 hours after surgery.

Consider referral to a specialist in asthma care for all patients with severe persistent and possibly moderate persistent asthma, as well as those who have had a life-threatening asthma exacerbation.

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48. PHARMACOTHERAPY

Kenneth J. Serio and Timothy D. Bigby

The pharmacologic treatment of asthma is composed of a heterogeneous group of bronchoactive agents. These include β_2-agonists, anticholinergics, theophyllines, cromolyn, nedocromil, leukotriene modifiers, and corticosteroids. The most notable changes in treatment over the last few years have been the increased use of inhaled corticosteroids and the introduction of leukotriene modifiers.

The primary method of medication delivery continues to be via the aerosolized route. This method is generally safe and associated with fewer side effects than when the same drugs are administered by other routes. The principal determinants of pulmonary aerosol deposition are (1) airway patency; (2) particle size (optimal particle size is 1–5 μm); (3) velocity of gas flow (the higher the velocity, the greater the impaction of particles in the upper respiratory tract); and (4) breath-holding time, which allows particles to sediment in the peripheral lung units. Metered-dose inhalers (MDIs), jet nebulization, or ultrasonic nebulization can aerosolize medications. Many recent studies suggest that MDIs and jet nebulizers are equally effective at achieving drug delivery and clinical response when equivalent doses are used and when the MDIs are used with a spacer device. The equivalency of these modes of delivery applies to clinical situations ranging from mild asthma exacerbation to status asthmaticus. Aerosol administration by a MDI with a spacer device is less expensive than nebulization, making MDIs the delivery method of choice in most clinical settings. Recent advances in medication delivery include the development of breath-actuated MDIs, multidose dry powder inhalers, and chlorofluorocarbon-free aerosol MDIs.

β_2-agonists remain the most popular agents used in the treatment of bronchoconstrictive airway diseases, including asthma and chronic obstructive pulmonary disease (COPD). β_2-receptors are distributed throughout the conducting airways and peripheral lung units. β_2-agonists bind to these receptors and induce airway smooth muscle relaxation; however, they also enhance mucociliary clearance, suppress microvascular leakage, inhibit inflammatory cell mediator release, and suppress the cough reflex. These drugs act at the β_2-receptor to produce bronchodilation; side effects include tremor and tachycardia. Paradoxical bronchospasm has been reported rarely; its pathogenesis is unknown. Short-acting β_2-agonists are generally considered *quick-relief* medications for acute symptoms; long-acting β_2-agonists are most useful as *long-term control* medications.

The inhaled, selective, short-acting β_2-agonists available in the United States include albuterol, pirbuterol, bitolterol, and terbutaline. The less selective β_2-agents, isoproterenol and metaproterenol, are no longer used commonly. Short-acting β_2-agonists have a rapid onset (5–10 minutes) and a short duration of action (3–6 hours). Fenoterol is a more potent but less selective β_2-agonist that has a somewhat longer duration of action. It is available only in Europe. Current asthma guidelines recommend the initial use of a short-acting β_2-agonist in the treatment of mild intermittent asthma. In addition, these agents should be used for prophylaxis in exercise-induced asthma and in the treatment of COPD.

Inhaled long-acting β_2-agonists include salmeterol in the United States and formoterol in Europe. Salmeterol has a slower onset of action (15–30 minutes) than the short-acting β_2-agonists and a much longer duration of action (up to 12 hours); consequently, this drug is not effective for control of acute symptoms but can be useful as part of a maintenance program. Safety profiles are similar between the short- and long-acting agents, and studies suggest no increased risk of toxicity exists when the medications are used concomitantly. Salmeterol has been shown to afford protection against bronchoconstrictor stimuli and no evidence is seen of a rebound increase in bronchial responsiveness after the cessation of salmeterol treatment. Long-acting β_2-agonists are particularly useful in the treatment of patients with nocturnal asthma, exercise-induced asthma, and aspirin-sensitive asthma. Studies indicate that the addition of salmeterol improves asthmatic control even in patients who are already

maintained on inhaled corticosteroids. Salmeterol has also been demonstrated to be better tolerated and more efficacious in the treatment of asthma than the long-acting theophylline preparations. Although some early studies explored the role of inhaled long-acting β_2-agonists as an alternative to inhaled corticosteroids, current guidelines indicate that inhaled corticosteroids should be added as the initial long-term control therapy in asthma.

Concerns over the safety of β_2-agonists derive from reports of death in association with the use of fenoterol and other short-acting β_2-agonists. Some data suggest that the regular use of these medications increases asthma morbidity and mortality, possibly by inducing drug tolerance. However, a critical review of these data suggest that results were likely confounded by other factors, such as asthma severity, delay in the initiation of other treatment, mode of drug delivery, and patient age. More recent data indicate that regular use of short-acting agents does not cause significant adverse effects. However, excessive use of short-acting inhaled β_2-agonists (>1.4 canisters per month) or a pattern of escalating administration are markers for increased asthma severity and indicate over-reliance on these drugs. Similarly, concerns about the induction of tolerance by the long-acting β_2-agonists or secondary delays in the institution of additional therapy have been investigated. Studies with exercise-induced asthma suggest that long-term salmeterol treatment affords sustained protection, but the duration of activity after a single dose decreases. Although the data are conflicting whether significant clinical tolerance occurs with use of the long-acting β_2-agonists, adverse effects on asthma morbidity and overall control of symptoms have not been demonstrated.

Oral β_2-agonists have been used to manage nocturnal asthma symptoms because of less fluctuation in drug levels and less frequent dosing. However, compared with inhaled preparations, the bronchodilatory effect of oral β_2-agonists is less and side effects are generally more prominent. Similarly, terbutaline and epinephrine are available for subcutaneous or intravenous administration, but studies in the emergency room setting suggest that parenteral administration of β_2-agonists results in no more pronounced bronchodilation and significantly greater side effects. Therefore, the use of parenteral β_2-agonists cannot be recommended.

Anticholinergic drugs have been used for centuries to treat bronchospasm. These atropinelike drugs antagonize muscarinic cholinergic receptors, decreasing intrinsic vagal tone of the airway and resulting in bronchodilation. The atropine derivative, ipratropium bromide, is available for delivery either as a MDI or nebulizer. Ipratropium is the only anticholinergic that is neither significantly absorbed systemically nor causes inspissation of secretions; thus, it is the only anticholinergic agent that should be used clinically. The anticholinergic drugs have been shown to block airway constriction in response to gastroesophageal reflux and airway irritants but not in response to allergen challenge or exercise. These agents can produce clinical benefit when used alone or as an adjunctive therapy to short-acting β_2-agonists in the treatment of asthma. However, the onset of action of the anticholinergic agents is generally slower than that of the β_2-agonists. Although the effectiveness of the anticholinergic drugs in the long-term management of asthma has not been rigorously examined, a subset of asthmatics does respond to these agents. They are also the treatment of choice for β-blocker–induced bronchospasm. The clinical utility of the anticholinergic agents is also well established in the treatment of COPD. When administered long term in the treatment of COPD, these medications have been demonstrated to produce improvement in baseline lung function and response to other bronchodilators. Inhaled ipratropium is generally considered safe with few observed side effects.

Theophylline, used for many years to treat airway disease, is available in multiple commercial preparations including oral, sustained-release preparations and intravenous aminophylline. Theophyllines are phosphodiesterase inhibitors and adenosine receptor antagonists; the mechanism of action at doses used clinically is not fully understood. Recent reports also suggest that theophylline can act to decrease leukotriene synthesis and modulate immune function. The physiologic effects of theophylline include bronchodilation, increased mucociliary clearance, decreased eosinophil infiltration of bronchial mucosa, and increased diaphragmatic muscle contractility. Long-acting, extended release theophylline preparations have proved to be efficacious in the

long-term management of asthma patients with predominantly nocturnal symptoms and are probably comparable to the long-acting β_2-agonists. Although theophylline does not appear to have increased benefit when added to β_2-agonists and corticosteroids in the treatment of an acute asthma exacerbation, its administration may be justified occasionally in patients with severe symptoms. Common side effects of theophylline include insomnia, nausea, arrhythmias, tremor, gastrointestinal symptoms, hypokalemia, gastroesophageal reflux, and central nervous system symptoms. Theophylline blood levels should be monitored regularly because of the narrow range between therapeutic efficacy and toxicity and because blood levels are altered by many commonly used medications.

Cromolyn sodium and *nedocromil* act by blocking chloride channels; animal studies also suggest that these agents can inhibit mast cell degranulation and inflammatory cell mediator release. However, the mechanism of action of these drugs in the treatment of asthma in humans is unclear. These drugs block the early and late asthmatic responses to allergen challenge, reducing asthma symptoms and decreasing the requirement for rescue β_2-agonist use. In maintenance therapy of asthma, the effects of these medications are generally not seen until at least 2 to 6 weeks of treatment and the response to this therapy is variable. These drugs have been used to treat aspirin-induced asthma, possibly by decreasing the synthesis of the cysteinyl leukotrienes. Additionally, they have been used to treat allergen- and exercise-induced asthma. Although the clinical response of asthma to both cromolyn and nedocromil is substantially less predictable than the response to inhaled corticosteroids, the safety of these drugs is well established and significant side effects are rare. Cromolyn and nedocromil have no role in the treatment of COPD. The high cost of these medications remains a major obstacle to their clinical use.

The *leukotriene modifiers* (leukotriene receptor antagonists and the 5-lipoxygenase inhibitors) have recently been introduced for the long-term control of asthma. Leukotrienes are lipid mediators that are derived from arachidonic acid via the 5-lipoxygenase pathway. They are released from inflammatory cells and mediate a variety of inflammatory responses, including increased vascular permeability, smooth muscle contraction, mucus hypersecretion, bronchial hyperreactivity, and eosinophil chemotaxis. The leukotriene modifier medications have been demonstrated to decrease the cellular infiltration of asthmatic bronchial mucosa. They have been shown to decrease asthma symptoms and the requirement for rescue therapy with short-acting β_2-agonists. In maintenance therapy of asthma, the leukotriene modifiers are effective in a smaller percentage of patients than inhaled corticosteroids, being efficacious in only approximately 50% of asthmatics. Likewise, in direct comparison studies, leukotriene modifiers have been found to be less potent than the chronic inhaled corticosteroids and equipotent to theophylline and the long-acting β_2-agonists. However, the use of leukotriene modifiers allows reduction in the maintenance dose of inhaled and oral corticosteroids (steroid-sparing) without a subsequent loss in asthma control. Moreover, a decrease in the requirement for oral corticosteroid rescue is observed in patients treated with leukotriene modifier agents.

The LTD_4 receptor antagonists, zafirlukast and montelukast (in the United States) and pranlukast (in Japan), have high oral bioavailability and require once- or twice-daily dosing. Although these medications are useful in maintenance therapy of many types of asthma, they have specific clinical utility in the treatment of patients with cough-variant asthma, exercise-induced asthma, and aspirin-sensitive asthma. The 5-lipoxygenase inhibitor, zileuton, is also available for the long-term control of asthma. This medication has been shown to be clinically useful in the treatment of patients with aspirin-induced and exercise-induced asthma.

Although the leukotriene modifiers are generally well tolerated, recent case reports have demonstrated an association between leukotriene receptor antagonist use and the development of the Churg-Strauss syndrome (eosinophilic vasculitis). However, studies note that corticosteroids were withdrawn in most of the reported cases, raising the likelihood that at least some of these cases were caused by unmasking of a previously unrecognized vasculitis during the tapering of the corticosteroids. Zileuton has been reported to cause elevated liver function tests in more than 4% of treated

patients. In addition, both the leukotriene receptor antagonists and zileuton have been reported to cause elevations in serum theophylline levels.

Corticosteroids are commonly used in the treatment of asthma because of their anti-inflammatory properties and established effectiveness. Their utility in asthma is dependent on the glucocorticoid activity. These compounds have been shown to decrease airway inflammation and hyperresponsiveness, inhibit the late response to allergen challenge, decrease the frequency of exacerbations, decrease the severity of asthma symptoms, and, possibly, decrease airway remodeling. However, among the most important early effects of corticosteroids are their ability to upregulate the expression and affinity of β_2-receptors in the lung. Side effects of these agents depend on the route of delivery. Although corticosteroids are effective in many asthmatic patients, corticosteroid-resistance has been reported in a small subset.

Inhaled corticosteroids are currently recommended as the initial long-term control therapy for asthma that is unresponsive to intermittent, inhaled short-acting β_2-agonists alone. The agents fluticasone, beclomethasone, budesonide, flunisolide, triamcinolone, and mometasone are currently available. These medications function to decrease airway inflammation and are effective in more than 70% of asthmatics. The inhaled corticosteroids have been shown to decrease the risk of asthma exacerbation and the risk for readmission after an acute exacerbation. In patients whose disease is poorly controlled by inhaled corticosteroids, the addition of a second long-term control medication (e.g., a long-acting β_2-agonist or theophylline) is superior to an increase in the inhaled corticosteroid dose. Side effects include cough, dysphonia, and oral thrush; however, the concomitant use of a spacer device and rinsing of the mouth after administration can minimize these effects. At high doses, inhaled corticosteroids can suppress the hypothalamic-pituitary-adrenal axis, but clinically relevant adrenal suppression is rare. The inhaled corticosteroids have also been reported to contribute to the development of cataracts and osteoporosis.

Systemic corticosteroids have been used widely in the treatment of asthma for many years. They can be administered orally (as prednisone and prednisolone), intravenously (as methylprednisolone), and intramuscularly (as triamcinolone). They have been shown to reduce the rate of hospitalization, shorten the duration of asthma exacerbation, and reduce the risk of relapse. Systemic corticosteroids are most often used initially at high dose, orally or intravenously, to treat the acute exacerbation. The drugs are subsequently tapered (generally over 3–10 days), although no evidence indicates that tapering after improvement decreases the risk of asthma relapse. In the case of prolonged administration of systemic corticosteroids, careful tapering is essential. The duration and frequency of therapy, as well as the dose, should be factored into the design of individual protocols for tapering. The presence of underlying conditions that can be exacerbated by corticosteroid use should also be carefully considered. Chronic use of systemic corticosteroids can result in pronounced side effects and toxicity, including myopathy, osteoporosis, hyperglycemia, dermal thinning, cataracts, weight gain, mood disturbance, Cushing's syndrome, and hypothalamic-pituitary-adrenal axis suppression. The corticosteroid withdrawal syndrome has also been reported with tapering corticosteroids in chronically treated patients.

Corticosteroid-sparing agents have been used in the treatment of refractory and corticosteroid-resistant asthma. Agents studied include cyclosporine, methotrexate, immunoglobulins, gold, troleandomycin, and hydroxychloroquine. Placebo-controlled trials have demonstrated that cyclosporine allows for a reduction in corticosteroid use and improves lung function. Likewise, randomized trials with methotrexate demonstrate a modest reduction in corticosteroid use. However, the risk of potential toxicity and further immunosuppression with these agents must be weighed carefully against the risk of continued corticosteroid use.

Other agents being studied for treatment of asthma include the cytokine antagonists or agonists, platelet-activating factor inhibitors, phosphodiesterase IV inhibitors, and nitric oxide synthase inhibitors. These agents are currently being investigated and are promising future therapies for asthma. Agents that have been studied with limited success in the treatment of asthma include inhaled loop diuretics, heparin, dapsone, and lidocaine.

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49. CHRONIC OBSTRUCTIVE PULMONARY DISEASE: DEFINITION AND EPIDEMIOLOGY

Andrew L. Ries

Chronic obstructive pulmonary disease (COPD) refers to a group of disorders that have in common the presence of persistent airflow obstruction. From the viewpoint of the pathologist, chronic bronchitis and emphysema are distinct processes—the former limited to the airways, the latter to the pulmonary parenchyma. From the viewpoint

of the clinician, such a distinction is difficult for several reasons: (1) Some degree of each may coexist in the same patient; *pure* forms of chronic bronchitis and emphysema are exceptions rather than the rule; (2) both are characterized by expiratory flow obstruction on simple spirometric testing; (3) patients with both processes often present with the same symptom—dyspnea on exertion; and (4) the presence of airway hyperreactivity (*asthma*, acutely reversible airways disease) in many patients with chronic bronchitis or emphysema further complicates the distinction. Faced with such complexities, it is understandable that the clinician often *lumps together* patients with chronic expiratory obstruction under the label *COPD*.

Nevertheless, distinct advantages are found in attempting to distinguish chronic bronchitis from emphysema—or at least to define the relative extent of each in a given patient. Such advantages relate particularly to the selection of therapy and to the natural history of these disorders, which is reflected in the individual patient's prognosis. For example, recent studies have indicated that mucous gland hypertrophy and mucus hypersecretion—both hallmarks of chronic bronchitis—are not major factors in causing airflow obstruction. Attempts at distinction are also essential to determine the pathogenetic differences between chronic bronchitis and emphysema, although the dominant role of cigarette smoking in both is clear.

The confusion between chronic bronchitis and emphysema has been compounded by the manner in which they have been defined by various scientific societies, in different studies, and in different nations. In defining chronic bronchitis and emphysema, three options are available: pathologic, clinical, and physiologic. In fact, all three options have been used. This is not surprising because pathologic evidence is rarely sought (or advisable) while the patient is alive; the physiologic techniques that allow distinction are still not generally applied; and attempts to provide clinical definitions were useful when neither pathologic nor physiologic criteria were available. Substantial progress has been made, however, in physiologic characterization of chronic bronchitis and emphysema and in correlating pathologic data with both physiologic and clinical observations.

Chronic bronchitis has long been defined in clinical terms. The most widely used definition is that of the American Thoracic Society, which defines chronic bronchitis as "a clinical disorder characterized by excessive mucous secretion...manifested by chronic or recurrent productive cough...on most days for a minimum of three months in the year and for not less than two successive years." This clinical definition is now known to have serious deficits. First, other disorders with similar manifestations must be excluded, such as bronchiectasis, tuberculosis, and lung abscess. Furthermore, patients with predominant asthma or emphysema may fit this definition. Finally, many patients with pathologic or physiologic hallmarks of chronic bronchitis may not qualify under this definition (i.e., they do not cough).

If pathologic findings were used to define chronic bronchitis, the task would be relatively easy. Pathologically, the hallmark of chronic bronchitis is the hyperplastic and hypertrophied mucous glands found in the submucosa of large cartilaginous bronchi. The ratio of bronchial gland thickness to bronchial wall thickness (Reid index) is increased. The small airways (noncartilaginous bronchioles < 2 mm in diameter) may also be involved, demonstrating mucous plugging, mural fibrosis and narrowing, goblet-cell hyperplasia, and inflammatory cell infiltrates. Thus, in the absence of parenchymal change, these findings in the airways would characterize *pure* chronic bronchitis.

Because such pathologic evidence is not conveniently available, much effort has been devoted to correlating pathologic data with physiologic tests. By physiologic testing, the pure chronic bronchitis patient should demonstrate:

1. Relatively normal total lung capacity (TLC) with modest elevation of the residual volume (RV) and functional residual capacity (FRC).
2. Some degree of expiratory and inspiratory flow obstruction (both flows are abnormal because airway narrowing is fixed anatomically).
3. Flow obstruction not acutely improved by bronchodilator administration.
4. Normal elastic recoil and compliance (pressure-volume curve of the lung).
5. Significant disturbances of gas exchange producing hypoxemia because of ventilation-perfusion imbalance. Hypercapnia can develop with more severe disease.
6. Normal diffusing capacity for carbon monoxide.

In contrast with the clinical description of chronic bronchitis, emphysema has long been defined in anatomic-pathologic terms. The widely used American Thoracic Society definition states that emphysema is present when there is "an anatomical alteration of the lung characterized by an abnormal enlargement of the airspaces distal to the nonrespiratory bronchioles, accompanied by destructive changes of the alveolar walls." Thus, pure emphysema is a parenchymal (airspace) disease in which the bronchi are not involved. In recent years, high resolution computed tomography has been used to detect emphysema based on anatomic changes in the lung parenchyma.

Pathologically, emphysema is characterized by disruption of the alveolar walls at some location within the acinus, which is the lung division distal to the terminal bronchiole that includes the respiratory bronchioles, alveolar ducts, and terminal alveoli. Depending on the dominant site of involvement, emphysema is defined pathologically as centrilobular (proximal acinar), in which the proximal part of the acinus is involved, or as panacinar, in which the whole acinar structure is involved.

A clinical definition of emphysema is lacking; if one did exist, it would be dominated by the historic finding of effort dyspnea.

Physiologically, patients with pure emphysema demonstrate distinct features:

1. The lung volumes show evidence of hyperinflation, namely, an elevated FRC, RV, and RV:TLC ratio. Often, TLC is increased. Early in the course of disease, vital capacity may be preserved (i.e., concomitant elevation in RV and TLC). With more severe disease, VC may be reduced in proportion to the elevation in RV. Such measurements are best made in a body plethysmograph, because the lung volume measured by gas dilution techniques (e.g., helium dilution, nitrogen washout) may underestimate the lung volume in emphysema.
2. Significant expiratory flow obstruction is present with preservation of inspiratory flows. This observation is most dramatically demonstrated by flow-volume curves that show normal flow rates during inspiration but severely reduced flow rates on expiration.
3. Expiratory obstruction is not immediately improved by bronchodilator administration.
4. Elastic recoil is low (i.e., low pleural pressures exist at TLC and other specified lung volumes) and compliance is increased (i.e., small pleural pressure changes are associated with large increases in lung volume). These findings are the physiologic correlates of alveolar disruption and are the hallmarks of emphysema.
5. Gas exchange is well preserved in the stable state, despite advanced spirometric abnormalities.
6. The diffusing capacity for carbon monoxide is reduced.

Therefore, to the extent that chronic bronchitis and emphysema exist in *pure* forms, they can be distinguished from each other and from asthma by physiologic tests that reflect the pathology involved. In practical terms, as already noted, mixed forms are the rule. This is particularly true when advanced disease is present.

Controversy exists about whether asthma itself is part of the spectrum of COPD. Nonspecific airway hyperresponsiveness has been proposed as a risk factor that predisposes smokers to developing COPD (the *Dutch hypothesis*). Asthmatic bronchitis is one of the recognized epidemiologic patterns of COPD. Asthma can result in chronic airflow obstruction and should probably be included within the clinical spectrum of COPD.

Chronic obstructive pulmonary disease is a major cause of death and disability. Because COPD is insidious, with a long latency period before clinical recognition, official statistics underestimate morbidity and mortality. As of 1990, COPD had moved up to the fourth leading cause of death in the United States. COPD was listed as the underlying cause of more than 106,000 deaths in 1996, accounting for approximately 4% of all deaths and contributing to an additional 5%. This represents an age-adjusted death rate of 21 per 100,000 in the population. In causes of death for persons 55 to 74 years of age, COPD ranks third among men and fourth among women. More than 95% of deaths from COPD occur after the age of 55 years. In contrast to other major diseases, death rates from COPD have increased considerably in recent years, 47% between 1979 and 1993.

In the United States, the overall prevalence is approximately 4% to 6% in men and 1% to 3% in women; in adults aged more than 55 years, COPD is recognized in approximately 10% to 15%. The 1994 National Health Interview Survey estimated that 14 million adults had chronic bronchitis and 2 million had emphysema. In that

year, the prevalence rates for COPD in older adults (>65 years of age) were 119/1000 in men and 97/1000 in women. Recent trends indicate that prevalence rates are stable to decreasing in men but increasing in women.

The impact of COPD on morbidity is even greater than on mortality. In the National Health Interview Survey in 1985, COPD accounted for 5% of doctors' office visits and more than 13% of all hospitalizations. COPD is a major cause of disability and reduced function among affected persons.

Epidemiologic studies have identified two main syndromes, with different risk factors and natural histories. The *usual* emphysematous form is associated closely with cigarette smoking. Patients develop airflow obstruction insidiously over many years, with minimal symptoms, followed by clinical disease in later years, with progressive symptoms and high morbidity and mortality. The second form of COPD, chronic asthmatic bronchitis, is associated with risk factors of atopy, high serum IgE, and bronchial hyperreactivity. Patients develop chronic airflow obstruction independent of smoking, although smoking can add risk. Asthmatic bronchitis is more amenable to medical therapy and has a better prognosis and survival than the emphysematous type.

Cigarette smoking is the major risk factor, accounting for nearly 90% of COPD cases. Compared with nonsmokers, current smokers have approximately 10 times the relative risk of developing COPD. The risk is equal for men and women. Previously, COPD was more common in men because of their higher smoking rates; in recent years, however, the disease has manifested more gender equality, reflecting similar smoking rates for men and women.

Marked individual variation in susceptibility is seen, and host factors play an important role. Only 10% to 15% of smokers develop significant obstructive lung disease. In susceptible persons, smoking is associated with an accelerated decline in lung function over many years that is related to the amount of smoking. Because of the large reserve in healthy lungs, disease is not typically recognized until later in life.

Exposure of nonsmokers to the smoke of others in an indoor environment (secondhand smoke) is associated with an increase in respiratory infections and lung disease in children and with modest changes in lung function in adults. However, it has not been clearly established that passive smoke exposure leads to clinically significant obstructive lung disease.

Some evidence indicates that environmental exposures (e.g., air pollution and occupational dusts and fumes) are harmful for persons with underlying lung disease and may increase the risk for developing COPD. However, it is unclear whether the effects are independent of smoking. Growing evidence also suggests that a history of childhood respiratory infections increases the risk for developing COPD in later life.

One credible theory about the pathogenesis of emphysema is that the disease results from an imbalance between lung proteases and antiproteases, enzymes that, respectively, promote injury and protect the lung against injury. Human neutrophil elastase (HNE) is released from granules of the neutrophil during phagocytocis and following stimulation, chemotaxis, and cell death. Cigarette smoke components appear to promote the release of (1) neutrophil chemotactic factors from alveolar macrophages and (2) HNE from neutrophils. The activity of HNE is mitigated by a serum protein, α_1-antiprotease α_1-Pi), which is synthesized by the liver and migrates freely into alveoli. Formulation of the protease/antiproteases theory of emphysema was catalyzed by the discovery that emphysema is common among individuals who are severely deficient in α_1-Pi, a globulin that is a potent inhibitor of several enzymes including trypsin and elastase. It is postulated that elastase, which is found in polymorphonuclear leukocytes and in alveolar macrophages, is normally released from these cells; larger quantities may be released in response to lower respiratory tract infections. When α_1-Pi is present, elastase is inhibited; in its absence, released elastase is free to digest the lung.

The gene for α_1-Pi deficiency is inherited in an autosomal recessive pattern—Pi MM is the normal phenotype, Pi ZZ the most common phenotype of homozygous deficiency. Although heterozygous persons have reduced levels of α_1-Pi, they do not have a clearly increased risk for developing disease. In congenital emphysema, anatomic changes predominate at the lung bases rather than in the upper lung fields. Less than 1 of 2000 individuals is severely deficient in α_1-Pi. More than 90% of the population—and the vast majority of patients with emphysema—are of the normal (MM) phenotype and have normal serum levels of α_1-Pi. Nevertheless, the same concept of enzyme-inhibitor bal-

ance may apply to other patients with emphysema. This possibility is supported by animal experiments in which emphysemalike disorders have been induced by intrapulmonary instillation of papain, elastase, and leukocyte homogenates. Evidence that a protease-antiprotease imbalance exists in the alveoli of patients deficient in α_1-Pi, and that this balance can be restored by intravenous administration of α_1-Pi, adds further weight to this hypothesis, as does the demonstration that certain oxidants (including components of cigarette smoke) can inactivate α_1-Pi, rendering it unable to inhibit elastase and other proteolytic enzymes.

It should be noted that the term *emphysema* is also applied to several conditions in which lung hyperinflation occurs without alveolar destruction. Among these conditions is congenital lobar emphysema, in which overinflation of a lobe (usually the left upper lobe) occurs, which can be life-threatening. Pathologically, overdistention of single or multiple lobes is seen. *Compensatory emphysema* is a term applied to overinflation of the remaining lung in the face of collapse, destruction, or resection of other lung zones. Partial obstruction of a major bronchus does not cause tissue destruction characteristic of emphysema, although it does result in overdistention of alveoli. *Senile emphysema* is a term applied to the normal modest overinflation of the lung that occurs with aging and is reflected in an increase in RV:TLC ratio, and is better referred to as the *aging lung*.

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50. CHRONIC OBSTRUCTIVE PULMONARY DISEASE: CLINICAL AND LABORATORY MANIFESTATIONS, PATHOPHYSIOLOGY, AND PROGNOSIS

Andrew L. Ries

Chronic obstructive pulmonary disease (COPD) typically presents later in life. Dyspnea is the hallmark symptom that brings the patient to medical attention and leads to a diagnosis. A careful history of the insidious onset of breathlessness on exertion, with or without a history of cough, sputum, or frequent lung infections, often provides the clue to diagnosis.

Because of the slow, progressive course of disease and the large reserve in lung function, a long preclinical period elapses during which the person who has smoked for years "without a problem" begins to note breathlessness with physical activities previously accomplished without difficulty. This may be attributed to "getting older" or "being out of shape." Reduced expiratory flow rates may be detected at this stage. Later, the patient may come to medical attention after a critical event, such as a winter cold from which recovery has been slow or has not occurred. Disease onset is often attributed to this time; in reality, however, this event just pushed the patient over the clinical edge of recognition, much like a rope weakened by progressive fraying breaks when *only* a small weight is attached.

Cough is a frequent symptom, often attributed to a *smoker's cough* early in disease. It is usually productive; sputum is described as mucoid. Finding is a history of frequent respiratory infections associated with increased cough, purulent sputum, and breathlessness. The patient may note that it takes longer than usual to recover from these infections.

Some patients with COPD develop abnormal gas exchange with hypoxemia or hypercapnia. Hypoxemia can be associated with cognitive or personality changes, polycythemia, and cyanosis. Chronic hypercapnia can cause headache, particularly on arising, and increased somnolence. During exercise, the arterial P_{O_2} may change significantly and unpredictably from the resting level. In many patients, the Pa_{O_2} decreases with physical activity; in others, it does not change or may actually increase.

On physical examination, decreased maximal expiratory flow may be apparent even in early disease. Therefore, it is important to assess maximal expiratory flow in persons at high risk (e.g., smokers). In early disease, the examination may be normal, but later, prolonged expiration or wheezing can be detected on forced exhalation. This can be assessed easily with the forced expiratory time, a useful screening test for expiratory obstruction. In this maneuver, the patient exhales with maximal effort through an open mouth after a full inspiration. The examiner listens with the bell of the stethoscope over the trachea in the suprasternal notch and records the time in seconds until airflow ceases. Normal persons can exhale completely within 4 seconds. A forced expiratory time greater than 6 seconds signifies significant expiratory obstruction.

Other physical signs of COPD are often not present until the disease becomes moderate to severe. Overinflation of the lungs can result in an increased anteroposterior diameter of the thorax and a low, flat diaphragm with reduced respiratory excursion. The flattened diaphragm contributes less to inspiration, placing more burden on the accessory breathing muscles (neck and intercostals) and producing greater respiratory movement in the upper chest. With severe hyperinflation, the diaphragm can even become inverted and move paradoxically—up on inspiration, down on expiration. This can be detected best with the patient supine, noting the inward movement of the lower rib cage and abdomen during inspiration. With advanced emphysema, the breath sounds are diminished because of reduced flow and increased lung inflation. Signs of pulmonary hypertension and right-sided heart failure (e.g., peripheral edema and hepatic congestion) are not usually detected until an advanced stage of disease.

The central diagnostic feature of COPD is reduced expiratory airflow, resulting from increased airway resistance because of airway narrowing. Spirometry is the standard pulmonary function test for measuring maximal airflow and is relatively simple, reliable, and reproducible. It is useful for detecting airflow obstruction, staging severity, and following the disease course. A reduction in the forced expiratory volume in 1 second (FEV_1) in relation to the forced vital capacity (FVC)—the FEV_1:FVC ratio—is a standard measure of obstruction. The FEV_1 is the best measure of disease severity; it correlates with exercise tolerance and survival. Other measures of expiratory airflow can also be helpful.

Measures of lung volumes reveal hyperinflation with an increase in residual volume, functional residual capacity, and, sometimes, total lung capacity. These tests can help to confirm the diagnosis suggested from spirometry. Emphysema causes a greater increase in total lung capacity than other obstructive diseases, as well as a reduced carbon monoxide diffusing capacity (DLCO), primarily because of the loss of alveolar-capillary surface area. However, DLCO is neither specific nor sensitive for emphysema.

Chest radiographs have limited usefulness in diagnosing or staging COPD; early in disease, they may be normal. Their main use is in detecting other parenchymal lung

or cardiovascular diseases that can present with similar symptoms. With advanced emphysema, the chest radiograph may reveal overinflation of the lungs with a low, flat diaphragm and an increase in the retrosternal airspace (anterior to the heart) on the lateral film. The emphysematous lungs may also appear radiolucent because of bullous changes and a paucity of vascular shadows. High-resolution computed tomography may be useful in documenting pathologic evidence of emphysema, but the clinical usefulness of this test is unproved.

Arterial blood gas analysis may reveal hypoxemia and hypercapnia, particularly in advanced disease. The relationship between gas exchange abnormalities and other measures of lung function is poor. Hypoxemia can worsen with exercise, sleep, or changes in body position.

The electrocardiogram is usually normal early in disease; later, signs may appear of right-sided heart strain, including right axis shift, increased R waves over the right precordial leads (V_1 and V_2), and peaked P waves (*P pulmonale*). These changes do not correlate well with the level of pulmonary hypertension.

Two characteristic clinical patterns of COPD were originally described by Dornholst: the *pink puffer* (type A or emphysematous type) and the *blue bloater* (type B or bronchitic type). Type A patients typically have severe dyspnea, with little cough and sputum. They are usually thin with a hyperinflated chest. Arterial blood gases reveal mild, if any, hypoxemia (i.e., *pink* without cyanosis) and normal to low arterial P_{CO_2} (i.e., *puffing* with increased breathing effort). Type B patients typically have a history of chronic bronchitis with cough, sputum, and recurrent exacerbations with respiratory tract infections. Dyspnea on exertion is a prominent symptom, but is often episodic. On examination, they tend to be overweight and cyanotic (*blue*) and have dependent edema, dilated neck veins, and hepatomegaly because of right ventricular failure (*bloated*). Auscultation of the lungs reveals diffuse expiratory and inspiratory rhonchi. Arterial blood gases demonstrate severe hypoxemia and hypercapnia with CO_2 retention (reflecting low ventilation). These differences may reflect variations in ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching and central respiratory drive.

In clinical practice, most patients with COPD have a mixture of type A and type B disease and fall between these two extremes. In addition, many patients with COPD have an element of asthma (i.e., reversible airways obstruction with bronchospasm). As discussed in chapter 49, more recent epidemiologic studies of COPD have identified two main syndromes with different risk factors and prognosis: emphysematous form and chronic asthmatic bronchitis.

The pathophysiologic basis of emphysematous disease is a consequence of slowly progressive alveolar fragmentation, loss of lung elasticity, and mechanically related expiratory airflow obstruction. If acute problems (e.g., infection, anesthesia, sedation, left ventricular failure) do not occur, the patient slowly becomes more breathless, inactive, and wasted. This decline can extend over a period of many years. The development of acute respiratory failure is usually an ominous sign, because it occurs near the end stage (i.e., when very advanced parenchymal destruction is present).

On the other hand, the patient with a more predominant bronchitis and asthmatic components of disease tends to have a more episodic course punctuated with exacerbations and reactive airway disease. Such patients tend to respond more to medical therapy and have a better prognosis.

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51. CHRONIC OBSTRUCTIVE PULMONARY DISEASE: MANAGEMENT

Andrew L. Ries

Chronic obstructive pulmonary disease (COPD) is by far a chronic, progressive, and irreversible disease, so the primary goals of management should be directed toward preventive health strategies to slow progression and reduce complications. Secondary goals are to improve symptoms and function and treat reversible components of the disease. Optimal management depends on the stage of disease. For patients with mild to moderate disease, early detection and diagnosis and counseling regarding appropriate preventive health strategies are important. For patients with moderate to severe disease, symptomatic treatment is also indicated.

Teaching the patient and family members how to participate in the patient's management as active partners with the physician is a key goal because it affects all the others. Patients who are adequately informed and motivated can work with the physician and maintain a level of function that the uninformed, poorly motivated, *passive* patient cannot.

Most patients with COPD are former or current cigarette smokers. Controlling smoking behavior is essential, regardless of the stage of disease. Smoking cessation will slow the rate of decline in forced expiratory volume in 1 second (FEV_1) and decrease coughing and sputum production. Naturally, the more advanced the functional loss, the less the impact will be. Therefore, early detection of COPD, particularly in smokers who are at high risk, and smoking cessation should be emphasized. Physicians play an important role by setting a smoke-free example in their lives and workplace. Physician advice is important and effective in inducing smokers to quit and maintain abstinence. Several studies have demonstrated that a physician who spends a few minutes inquiring about smoking status and providing advice to quit can achieve abstinence rates of up to 10% to 20% at 1 year. The use of additional modalities such as a comprehensive smoking cessation program and nicotine gum, nicotine dermal patches, or clonidine patches can lead to long-term cessation rates of as high as 50% in motivated patients.

Pulmonary infection is the most common complication in COPD. Prophylactic influenza vaccination should be administered annually, preferably in the early fall. Pneumococcal vaccination, with the expanded version (containing the capsular polysaccharide of 23 serotypes), should be administered every 5 to 10 years. As effective antiviral agents become available (e.g., amantadine), consider their use for the patient with COPD, particularly during epidemics of influenza A.

Another preventive approach is to assess patient exposure to occupational-environmental air pollutants and, if possible, eliminate or reduce the patient's exposure to them. A final method used to prevent complications is to avoid therapies and drugs that can compromise patient function. Patients with COPD tend to become vic-

tims of polypharmacy. To avoid this problem, carefully consider the risk-to-benefit characteristics of each therapy (drug, oxygen, or mechanical device) before it is instituted. Constantly review the treatment regimen, deleting elements that have been of no benefit, particularly if they can induce long-term toxicity.

For patients with recognized COPD, pharmacotherapy is directed toward the reversible component of airway obstruction and control of secretions. Bronchodilators used to improve symptoms and increase airway caliber include sympathomimetic β-agonists, anticholinergics, and methylxanthines (theophylline). The decision to treat a patient with a bronchodilator should not depend on demonstrating an acute response, as many patients respond to regular therapy. Airway hyperreactivity is common in patients with COPD and chronic therapy with bronchodilators can serve to prevent airways constriction caused by inhaled irritants. Also, these medications may have effects beyond just bronchodilation.

Sympathomimetic bronchodilators are used commonly. Newer β_2 agents are more selective and longer-acting and have fewer side effects than older, nonselective drugs. The preferred method of administration is by inhalation with a metered-dose inhaler (MDI). This produces more bronchodilation with fewer side effects than oral or other systemic routes. Used properly, a MDI is equally effective and less expensive than a liquid nebulizer and can be used in acute and emergency department settings. Extensions or spacers may help persons who have difficulty coordinating the MDI, particularly children and older adults. The key to MDI use is proper technique. All patients should be instructed and observed in following several key steps in using MDIs: (1) shake inhaler, remove cap, hold upright; (2) exhale to functional residual capacity or below; (3) place inhaler 2 to 4 cm in front of open mouth; (4) activate inhaler just after the start of a slow, deep inhalation; (5) hold breath for 5 to 10 seconds; (6) exhale slowly; and (7) wait at least 1 minute before next puff. In addition to bronchodilation, β-agonists can also reduce airway hyperresponsiveness and enhance mucociliary clearance. The most common side effects are tachycardia and skeletal muscle tremor.

Anticholinergics have recently gained prominence in the treatment of COPD. Although their bronchodilating effects have been known for many years, the selectivity and reduced side effects of newer agents (e.g., ipratropium bromide) have increased their usefulness. Bronchodilation is thought to be caused by inhibition of cholinergic-mediated bronchomotor tone. The drugs are reported to be more effective in larger airways, making them particularly useful for patients with COPD. They can be used concomitantly with β_2 agonists.

Theophylline preparations have been used in treating patients with COPD for many years, but their use has decreased because of a narrow toxic-therapeutic margin, frequent problems with toxicity, and the advent of newer, more selective bronchodilating agents. The mechanism of bronchodilation from theophylline is still not clearly defined. Theophylline has other potentially beneficial effects such as improved diaphragmatic function, reduced dyspnea, increased mucociliary clearance, and stimulation of respiratory drive. Because of individual variability in metabolism and the many factors that can alter metabolism (e.g., drugs such as cimetidine, erythromycin, and ciprofloxacin), blood levels must be monitored with chronic therapy. The target therapeutic level is typically 10 to 20 μg/ml. Minor side effects such as tremor, insomnia, irritability, and gastrointestinal upset can occur with levels well below 20 μ/ml. More serious side effects, including vomiting, dysrhythmias, hypotension, and seizures, generally develop at higher blood levels. Older patients are particularly susceptible to toxicity.

Corticosteroids can be beneficial for some patients with COPD. The complications of long-term use are well known and chronic use of systemic corticosteroids should be avoided, if possible. A meta-analysis of 16 clinical trials of oral steroid therapy for stable patients found that a 20% improvement in FEV_1 occurred in approximately 10% more patients on steroids than on placebo. Many patients on corticosteroids report subjective symptom improvement, but long-term steroid use is associated with many serious side effects. A limited trial of corticosteroids is probably justified in patients who cannot be managed with standard bronchodilators alone. A single morning dose of prednisone (20–40 mg) for 5 to 7 days is a typical starting point. Treatment beyond a few weeks should be continued only with a significant improvement in pulmonary function and symptoms. For long-term therapy, the dose should be kept as low as possible

to minimize side effects. Inhaled steroids, best used through a spacer device to minimize oral deposition, are safer, but their effectiveness in COPD has not been clearly established—although several ongoing multicenter clinical trials are evaluating the role of inhaled corticosteroids in the management of COPD.

For patients with chronic cough and sputum, techniques to control secretions are important. Patients should be encouraged to drink several glasses of fluid per day, but excessive hydration is not warranted. They should also be taught the technique of controlled coughing, which involves a deep inspiration, breath-holding for a few seconds, and then coughing two or three times. Postural drainage is effective in patients with heavy sputum production. The use of mucolytic agents to thin secretions and promote clearance is controversial. Theoretically, therapy with drugs such as oral iodinated glycerol, nebulized acetylcysteine, or, more recently, recombinant human deoxyribonuclease, works best in thinning secretions that are thick, mucoid, and heavy. Whether this produces physiologic or symptomatic improvement is unclear. Cough suppressant therapy is generally not recommended, as cough is an essential protective mechanism.

Because of impaired mucociliary clearance and less effective cough, secretions can pool in dependent portions of the lung and be difficult to clear. For acute exacerbations, when sputum changes color and increases in volume, treatment with antibiotics is indicated. In many cases, a specific bacterial pathogen cannot be identified from purulent sputum. For such episodes of acute bronchitis, it is appropriate to institute a course (7–10 days) of antibiotics empirically without a sputum culture. Oral antibiotics such as trimethoprim-sulfamethoxazole, ampicillin, amoxicillin-clavulanate, tetracycline, or erythromycin are commonly chosen to cover pathogens colonizing the respiratory tract, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

In the severely hypoxemic patient, oxygen therapy has been shown to improve survival and reduce morbidity from consequences such as right ventricular failure, polycythemia, and psychologic-mental dysfunction. Less clearly defined are the possible benefits of supplemental oxygen for nonhypoxemic patients or for patients with hypoxemia only under certain conditions (e.g., exercise, sleep). The results of two multicenter clinical trials (one in Great Britain, the other in the United States) justify long-term oxygen therapy for patients with significant resting hypoxemia (arterial $Po_2 \leq 55$ mm Hg or $So_2 \leq 88\%$). For patients with an arterial Po_2 between 56 and 59 mm Hg, oxygen is indicated in cases of erythrocytosis (hematocrit 55 or more) or cor pulmonale. The decision for long-term therapy should be made only in stable patients on optimal treatment for at least 30 days. Patients recovering from an acute illness should be reevaluated after a period of stability before committing to this expensive treatment. Several options exist for long-term oxygen therapy. Home-care providers, respiratory therapy personnel, and pulmonary rehabilitation professionals are excellent sources of information about available options, including gas sources (e.g., liquid, compressed gas, concentrators) and delivery devices (e.g., nasal, transtracheal, or conserving catheters and inspiratory demand regulators). Hypoxemic patients living at high altitude may benefit by moving to sea level, where the ambient oxygen tension is higher. If air travel is contemplated, arrangements may be necessary for supplemental oxygen because commercial aircraft cabins are pressurized at 5000 to 8000 feet.

Patients with right ventricular failure often respond to gentle diuresis and the initiation of chronic oxygen therapy. Digitalis may be useful if left ventricular failure is present; however, its role, if any, in pure right ventricle failure has not been established. Phlebotomy has long been advocated for the treatment of polycythemia. Patients often report an immediate subjective improvement in their dyspnea and some improvement in their exercise tolerance. However, objective evidence for long-term improvement in lung function and hemodynamic indices is lacking.

The role of surgery in COPD is being reevaluated. Bullectomy may benefit selected patients with large space-occupying bullae. The role of laser ablation of bullae remains to be defined. Lung transplantation for COPD is feasible and has been performed in many centers; criteria for selection and long-term follow-up are still evolving. In recent years, lung volume reduction surgery has been advocated for patients with advanced emphysema but is yet of unproved benefit. Currently, a national, multicenter trial (National Emphysema Treatment Trial, co-sponsored by the Health Care Financing

Administration and the National Institutes of Health) is being conducted to evaluate lung volume reduction surgery.

Pulmonary rehabilitation is an established preventive health strategy that enhances standard therapy for persons with chronic lung disease to control and alleviate symptoms, optimize function, and reduce the medical and economic burdens of disease. Multidisciplinary programs include education, respiratory and chest physiotherapy instruction, psychosocial support, and exercise training. As with other rehabilitation programs, the primary goal is to restore the patient to the highest possible level of independent function. This can be accomplished by helping patients become more knowledgeable about their disease, more actively involved in their own healthcare, more independent in daily care activities, and less dependent on family, friends, and health professionals and other expensive medical resources. Benefits of pulmonary rehabilitation include improved exercise tolerance and symptoms and reduced hospitalizations and use of expensive medical resources. Patients report improved quality of life with a reduction in respiratory symptoms, an increase in exercise tolerance and ability to perform physical activities of daily living, and improved psychological function, with less anxiety and depression and increased feelings of hope, control, and self-esteem.

Breathing retraining techniques include instruction in pursed-lip breathing and breathing patterns. Pursed-lip breathing imparts a subjective relief of dyspnea in some individuals. In theory, it prevents airway collapse during expiration. Pursed-lip breathing is often accompanied by an instantaneous diminution in activity of the accessory muscles of respiration. Slow, deep breathing often provides a subjective sense of improved respiratory control. The increased tidal volume can serve to reduce wasted ventilation.

Formal rehabilitation programs have obvious advantages for both patients and physicians. But, however achieved, patient education is essential. Patients who understand their disease, medications, and the other elements of their regimen are likely to avoid hospitalization and a variety of other untoward events.

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52. PULMONARY REHABILITATION

Andrew L. Ries

Comprehensive pulmonary rehabilitation programs (PRPs) are well established as a means to enhance standard medical therapy and reduce disability for patients with chronic lung diseases. The primary goal is to restore the patient to the highest possible level of independent function. This can be accomplished by helping patients to become more knowledgeable about their disease, more actively involved in their own

healthcare, more independent in performing daily care activities, and, therefore, less dependent on family, friends, health professionals, and expensive medical resources.

The typical program includes multidisciplinary participation by physicians, nurses, respiratory and physical therapists, exercise specialists, psychologists, and other healthcare professionals with particular expertise. The program should be tailored to the needs of the individual patient. To be successful, it should address important emotional and psychosocial problems as well as help to optimize medical therapy to improve lung function. The role of the rehabilitation program is to provide support for the patient, family, and primary care physician.

Any patient with symptomatic chronic lung disease can be a candidate for pulmonary rehabilitation. The greatest experience with pulmonary rehabilitation has been in patients with chronic obstructive pulmonary disease (COPD); however, patients with other chronic lung diseases should also be considered. Pulmonary rehabilitation has also been found to be a beneficial adjunct to surgical programs such as lung transplantation and lung volume reduction surgery.

Appropriate patients are those who recognize their symptoms are caused by lung disease, perceive impairment or disability related to that disease, and are motivated to be active participants in their own care to improve their health status. Patients should be stabilized on standard medical therapy and evaluated carefully before entering a program so that appropriate and realistic goals can be set. Pulmonary function tests are used to characterize and quantify the lung disease. Exercise testing helps to assess initial exercise tolerance, evaluate possible blood gas changes (e.g., exercise-induced hypoxemia), and plan a safe and appropriate training program.

The components of a comprehensive pulmonary rehabilitation program include education, instruction in respiratory chest physiotherapy techniques, psychosocial support, and exercise training.

Educating patients and family members about lung disease and teaching them specific ways to deal with problems are essential. Educated patients are better able to cope with their disease, easier to deal with, and more likely to avoid unnecessary visits to physicians' offices, emergency departments, and hospitals. Patients should be taught appropriate chest and respiratory therapy techniques. Proper coughing and postural drainage techniques are important for all patients, especially those with excess mucus production. Techniques of pursed-lip and diaphragmatic breathing and relaxation training help to improve ventilatory efficiency and assist patients in gaining control over the frightening symptom of dyspnea. Patients with respiratory therapy equipment should be instructed in its proper use, care, and cleaning. Patients with significant hypoxemia should be evaluated for optimal methods of continuous oxygen therapy and instructed in its proper use because oxygen therapy has been shown to improve survival and to reduce morbidity for these patients.

Patients with chronic lung disease have significant psychosocial problems as they struggle to cope with symptoms that are often poorly understood. They become depressed, frightened, anxious, and more dependent on others to care for their needs.

Progressive breathlessness leads to a vicious *fear-dyspnea* cycle in which increasing dyspnea produces more fear and anxiety which, in turn, leads to more dyspnea. In a pulmonary rehabilitation program, these problems can be dealt with effectively by enthusiastic and supportive staff who can communicate with, understand, and motivate these patients. Important family members and friends should be included in program activities. Support groups and group therapy sessions are also effective. Patients with severe psychiatric disorders may benefit from individual counseling and psychotherapy. Psychotropic drugs should generally be reserved for patients with severe levels of psychological dysfunction.

Exercise training provides both physiologic and psychological benefits and is an ideal opportunity for patients to practice methods for controlling dyspnea. The exercise program should be safe and designed appropriately for each patient's interest, environment, and level of function. Walking programs are particularly useful and have the added benefit of encouraging patients to expand their social horizons. Other types of exercise (e.g., cycling, swimming) are also effective. Because many patients with chronic lung disease have limited exercise tolerance, emphasis during training should be placed on increasing endurance—that is the time of sustained work. Exercise training of the

upper extremities may be beneficial for the many pulmonary patients who report disabling dyspnea for daily care activities involving the arms (e.g., lifting, grooming) at work levels much lower than for the legs.

In recent years, increased attention has been drawn to peripheral muscle dysfunction in patients with chronic lung disease and the role of muscle fatigue as a limitation to exercise tolerance. This has stimulated new research initiatives in this area. Specific peripheral muscle strength and endurance training regimens have been developed and incorporated into pulmonary rehabilation programs (PRPs). The potential role of respiratory muscle fatigue in pulmonary patients has led to attempts to train the ventilatory muscles. Although the ventilatory muscles can be trained successfully, the role of this type of training in improving exercise performance has not been clearly established.

Exercise-induced hypoxemia occurs unpredictably in patients with COPD who may not be hypoxemic at rest. Hypoxemia is not a contraindication to exercise training. Such patients can be given convenient, portable systems for ambulatory oxygen so that exercise can be performed safely.

The results of comprehensive PRPs have demonstrated significant benefits for patients with COPD and other lung diseases. As an effective, preventive healthcare intervention, pulmonary rehabilitation has proved to be cost-effective in decreasing both hospitalization days and the use of expensive medical resources. After rehabilitation, patients have an improved quality of life, reduced symptoms, increased exercise tolerance, more independence, increased ability to perform activities of daily living, and improvement in psychological function, with less anxiety and depression and increased feelings of hope, control, and self-esteem. Even after a short-term intervention, benefits typically last for at least 1 to 2 years.

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53. BRONCHIECTASIS

Julian P. Lichter

Bronchiectasis is usually defined in anatomic terms as a persistent and irreversible dilatation and distortion of medium-sized bronchi. The entity was first described by Laennec in 1819. Bronchi can be dilated temporarily (e.g., following pneumonia, with atelectasis, tracheobronchitis, or temporary airway obstruction) and then return to normal size after several weeks or months. Following bacterial pneumonia, repeat bronchograms will show resolution of dilated bronchi in 90% of cases after 3 months. This, however, is not true of bronchiectasis.

It is now generally accepted that bronchiectasis is an acquired disease process that develops in early childhood or later, rather than a congenital abnormality present at birth. Bronchiectasis is not a discrete disease entity but rather the end stage of a variety of unrelated pulmonary insults and antecedent events. All, however, require an infectious insult and impairment of drainage, airway obstruction, or a defect in host defense.

Bronchiectasis has been classified in numerous ways: (1) on the basis of putative pathogenetic mechanisms; (2) by gross and microscopic pathologic findings; (3) by bronchographic anatomy; or (4) by predisposing causative factors. The most enduring anatomic classification is that of Reid (1950), who correlated pathologic changes with bronchography for the first time. Three different appearances were described: *Cylindrical bronchiectasis* refers to bronchi that are uniformly dilated and do not taper, but rather end abruptly. This is due to plugging of smaller bronchi by thick mucus and casts. The bronchi are dilated to greater than 2 mm but can be so large as to admit a finger. *Varicose bronchiectasis* describes dilated bronchi with irregular, bulging contours reminiscent of a varicose vein. They do not taper and terminations are bulbous. Bronchial subdivisions are reduced. *Cystic or saccular bronchiectasis*, the most severe form, is characterized by sharply reduced bronchial subdivisions and dilated bronchi ending in cystic, pus-filled cavities. *Saccules* may occur at the fifth subdivision (normally approximately 20 subdivisions exist), with the more peripheral bronchial branches destroyed and fibrosed. All three forms can be present in the same patient. Each anatomic type of bronchial dilatation has been shown to be potentially reversible, including saccular changes.

The pathogenesis of bronchiectasis has not been fully elucidated, but the key element appears to be inflammatory destruction of the muscle, elastic tissue, and cartilage of the bronchial wall by infected mucopus in close and prolonged contact with the bronchial wall. Mucopus contains neutrophilic products capable of damaging lung tissue (serine proteases and toxic oxygen radicals), as well as nitric oxide, inflammatory cytokines (e.g., interleukin 8), and substances that interfere with ciliary movement

and mucociliary clearance. Build-up of such infected secretions often occurs distal to obstruction by inspissated mucous plugs with accompanying postobstructive atelectasis. A focal obstruction may occur to a segment or lobe by an aspirated foreign body, cancer, or surrounding lymph nodes (follicular bronchiectasis causing the classic middle lobe syndrome). An infected mucocele develops with subsequent mechanical dilatation of bronchi already weakened by proteolytic attack. The initial inflammatory insult is followed by secondary bacterial colonization, which produces further bronchial wall damage and predisposes to further colonization, thus setting up a vicious cycle. Eventual fibrosis of bronchial walls and surrounding lung is postulated to result in traction on the weakened flabby bronchial walls, thus contributing to their distention. Distention can also be aggravated by surrounding atelectatic lung, which allows the bronchi to be more affected by intrathoracic pressure swings.

Pathologically, the endobronchial mucosa is denuded and may be replaced by nonciliated, low cuboidal or squamous epithelium. Fragmentation and destruction of the muscular, elastic, and cartilaginous components of the bronchial wall occurs. Affected airways become tortuous and flabby. Areas of mucosa are eroded and microabscesses form, with the eventual development of cystic sacs of pus. In chronic, long-standing bronchiectasis, marked fibrosis occurs in and surrounding the bronchial walls. Bronchial arteries may also be considerably enlarged (up to three times normal caliber) and tortuous, forming extensive anastomoses with the pulmonary circulation.

The incidence of the more severe forms of bronchiectasis (i.e., multilobar involvement with voluminous purulent or fetid sputum) has declined in the Western world since the advent of the antibiotic era. Symptomatic bronchiectasis, nevertheless, is still prevalent today in less severe forms and, especially, in patients with underlying congenital diseases. Many patients with diagnosed chronic bronchitis with chronic sputum production, recurrent acute exacerbations, or both may well have underlying undiagnosed bronchiectasis. Clinically, these two pathologic processes may be indistinguishable.

Bronchiectasis is bilateral in approximately 30% of patients. The left lower lobe is involved about three times more frequently than the right lower lobe, probably because the left mainstem bronchus is slightly narrower. Dependency enhances the likelihood of involvement because drainage of secretions is impaired. The left lower lobe is the most common site, followed by the lingula and right middle lobe.

The predisposing causative factors can be divided into those causing focal versus diffuse disease. Focal causes are mostly secondary to bronchial obstruction (i.e., aspiration of a foreign body, carcinoma, surrounding lymph nodes, or inspissated viscid secretions). Diffuse bronchiectasis is usually associated with previous widespread pneumonias, chronic granulomatous diseases, hypersensitivity and immunodeficiency disorders, genetic syndromes, and certain rheumatic diseases.

Pneumonias are either primary viral or secondary bacterial pneumonias following viral infections (especially during childhood). Pertussis and measles were very common antecedents of follicular bronchiectasis before immunization for these diseases. Severe influenza, varicella pneumonia, and repeated mycoplasma infections can also result in bronchiectasis. Bacteria that cause necrotizing pneumonias, such as *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas*, and anaerobes (following aspiration), can cause saccular bronchiectasis. Once bronchiectasis is present, only then will *Haemophilus influenzae* be found in sputum during exacerbations, contributing to further bronchial damage.

In allergic bronchopulmonary aspergillosis, bronchial dilatation occurs in more proximal bronchi as a result of type III immune complex reactions.

A frequent cause of bronchiectasis today is the spectrum of granulomatous diseases: tuberculosis, sarcoidosis, histoplasmosis, and coccidioidomycosis. Tuberculosis is classically associated with bronchiectasis affecting mainly the upper lobes. Tuberculosis is also the most common cause of the middle lobe syndrome, in which obstruction of the normally slitlike middle lobe bronchial orifice by inflammatory lymph nodes occurs. Several reports have been made of presumed normal hosts (usually nonsmoking women over the age of 50 years) who have developed bronchiectasis with primary *Mycobacterium avium* complex infections.

Bronchiectasis can be a manifestation of congenital (X-linked agammaglobulinemia, IgG_2 subclass deficiency) or acquired (chronic granulomatous disease) immunodeficiency

states. The recent recognition of bronchiectasis in the acquired immunodeficiency syndrome illustrates the accelerated destructive interaction between repeated infections and impaired host defense.

An array of genetic defects are associated with clinical syndromes in which bronchiectasis is often prominent. Cystic fibrosis, Mounier-Kuhn syndrome (tracheobronchomegaly), Williams-Campbell syndrome (bronchial cartilage deficiency), Kartagener's syndrome (situs inversus, paranasal sinusitis, and bronchiectasis), Young's syndrome (obstructive azoospermia and chronic sinopulmonary infection), and immotile cilia syndrome (abnormal ciliary ultrastructure and function) are examples of such congenital disorders. All of these conditions predispose to recurrent lower respiratory tract infections as a result of poor tracheobronchial clearance.

Two rheumatic diseases, rheumatoid arthritis and Sjögren's syndrome, can be complicated by bronchiectasis. The arthropathy and sicca features are usually advanced when the bronchiectasis becomes apparent.

Clinically, it is important to realize that not all anatomically demonstrable areas of bronchiectasis are the cause of symptoms. In fact, symptomatic bronchiectasis is much less common than anatomic asymptomatic bronchiectasis, which may never require treatment. Where bilateral or multilobar involvement is demonstrable and the patient is symptomatic, the symptoms can be caused by involvement of only one segment or lobe. This has important implications for surgical treatment options: It is not necessary to excise asymptomatic bronchiectatic areas on the presumption that these will eventually be the sites of recurrent infection. Conversely, the anatomic demonstration of bilateral bronchiectasis may not necessarily rule out successful surgical excision of one symptom-producing lobe or segment. A recent study suggests that "indium labeled white blood cells may be useful in identifying those bronchiectatic segments which are in fact infected and presumably responsible for symptoms."

Bronchiectasis can manifest clinically in a number of well-described ways. The classic presentation is one of chronic cough and copious purulent or mucopurulent sputum (*wet* bronchiectasis). Sputum production may be continuous, with intermittent febrile exacerbations during which both cough and expectoration increase, or the patient can have quiescent periods punctuated by frequent recurrences. Isolation of mucoid *Pseudomonas* organisms should suggest the diagnosis of bronchiectasis rather than chronic bronchitis. Alternatively, the patient may present with recurrent, discrete infections arising from the same segment or lobe. This suggests a structural abnormality in the area of the lung, which could be caused by bronchiectasis. A third presentation is that of recurrent, dry cough associated with intermittent episodes of hemoptysis (*dry* bronchiectasis). Usually, a remote history is found of granulomatous infection, especially tuberculosis, and the upper lobes are often affected primarily, allowing for good drainage. A mild respiratory infection not infrequently precedes the hemoptysis. Episodes of hemoptysis can occur months or years apart. Hemoptysis can be life-threatening, because bleeding is from bronchial vessels with systemic pressures. Hemoptysis eventually complicates 50% of cases of bronchiectasis. Wheezing and dyspnea can complicate bronchiectasis and become more persistent as the disease progresses. Pleuritic chest pain may be a prominent symptom, indicating a recurrent respiratory infection. Sinusitis is commonly associated with bronchiectasis (~50%).

Physical examination often reveals a localized area of persistent, coarse, *moist* crackles. In the preantibiotic era, clubbing, cyanosis, cor pulmonale, cachexia, and secondary amyloidosis were common, but these are rarely observed today.

The chest radiograph can be normal in 7% to 20% of patients with established bronchiectasis. Radiographic abnormalities are rarely distinctive or diagnostic. The diagnosis is supported by increased or crowded lung markings, tubular or *ring* shadows (produced by thickened dilated bronchial walls), *gloved finger* shadows, and, especially, cystic air-containing areas with or without fluid levels. High-resolution computed tomography (CT) has become the most reliable modality in the evaluation and noninvasive diagnosis of bronchiectasis. Recently published studies using thinner sections at close interslice intervals indicate that both sensitivity and specificity were higher than 95% in the diagnosis of cylindrical bronchiectasis. An airway diameter of more than 1.5 times the adjacent blood vessel is indicative of cylindrical bronchiectasis. Other anatomic forms are even easier to diagnose on CT.

The diagnostic approach to a patient in whom is seen a strong suggestion of bronchiectasis on the basis of chronic cough, sputum, recurrent focal infection, or hemoptysis includes x-ray study, sputum smear and culture, pulmonary function testing (which should show a picture of airway obstruction), immunologic evaluation, sweat test, CT and, possibly, bronchography. A presumptive diagnosis can usually be made on the basis of the clinical history, examination, and the aforementioned tests, although, as mentioned, chronic bronchitis may be indistinguishable on purely clinical grounds.

A medical program can then be instituted that should include hydration, postural drainage and chest percussion, bronchodilators, possibly steroids, and, most importantly, appropriate antibiotic therapy. A higher than usual dosage of antibiotics may be required for prolonged periods (i.e., months) to adequately reduce the colonizing microbial load and to break the vicious circle whereby build-up of purulent, elastase-positive, ciliotoxic secretions results in increasing tissue damage, worsening bronchiectasis, and further predisposition to infection. Pre-emptive or suppressive antimicrobial treatment may need to be given at regular intervals or even continuously, rotating the antibiotics to reduce the emergence of resistant organisms, although the efficacy of these regimens is less well-studied. Aerosolized antibiotics (especially tobramycin for chronic *Pseudomonas* infection) have been used effectively and safely in bronchiectasis. Ongoing studies are evaluating long-term safety (i.e., emergence of resistant organisms). Recent data suggest the beneficial effects of various secretion-loosening and enhanced secretion-removal maneuvers in patients with bronchiectasis. These include the use of oral bromhexine, inhaled acetylcysteine, cold-water jet nebulizing humidification of inspired air or oxygen during chest physiotherapy, and aerosolized recombinant human deoxyribonuclease (effective only in patients with cystic fibrosis). Inhaled steroids have also been shown to reduce daily sputum production (by 18%) and to reduce cough significantly.

Many patients do well with a tightly controlled program of medical management as described above. Some, however, remain significantly symptomatic and debilitated. These patients deserve consideration for surgical options. In the years since the advent of potent antibiotics, a swing has occurred toward a somewhat restricted role for surgery. Some surgical series with extensive experience appear to challenge this conservative approach. Many surgeons believe that the success of medical therapy in patients with minimal or moderate disease has obscured the current role of surgery in patients with advanced bronchiectasis, resulting in delays in appropriate treatment. Resection of multilobar and bilateral disease has been successful with low mortality and morbidity rates in carefully selected patients, if the lung tissue being resected is already shrunken and functionless and if compensatory expansion or hypertrophy of the remaining normal lung exists preoperatively. It has also been observed in many cases that resection of severe areas of bronchiectasis on one side resulted in such an improvement in symptoms that subsequent planned resection of contralateral disease was then put on hold. In some patients, therefore, a place is seen for resection of a bronchiectatic *sump* area that is causing severe symptoms, ignoring other lesser-involved areas that are not causing symptoms.

A recent surgical study recommends, however, that resection should be limited to patients with localized disease unless life-threatening symptoms are present. Complete resection should be performed whenever possible to achieve maximal benefit. Complete pneumonectomy for bronchiectasis should be avoided as the mortality rate is high (43%).

High-quality bilateral bronchograms or CT scans should be performed before any resectional surgery to determine the exact extent and severity of the bronchiectatic changes.

All patients should have a preoperative bronchoscopy to rule out obstruction by stricture, foreign body, or neoplasm and to determine the degree of inflammation in the bronchial wall, which if severe can negate resection until better infection control has been achieved. The major goals for surgery in bronchiectasis are to improve the quality of life for those patients who have failed medical treatment by (1) removal of destroyed lung partially obstructed by a tumor or the residue of a foreign body; (2) reduction in acute infective episodes; (3) reduction in overwhelming purulent and viscid sputum production; (4) removal of an area suspected of harboring resistant organisms (e.g., *Mycobacterium avium complex* or *Aspergillus*); and (5) elimination of bronchiectatic air-

ways subject to uncontrolled hemorrhage. If an interventional radiology service is available, bronchial artery embolization is the initial treatment of choice for intractable bleeding caused by bronchiectasis, because it will preserve lung tissue and eliminate the need for a thoracotomy. Surgery may still be necessary if bleeding persists.

Young patients with severe, progressive bronchiectasis, uncontrolled by conservative measures, and with lung function too severely impaired to tolerate resection may now be candidates for lung transplantation. Currently, bilateral, sequential lung transplantation is the procedure of choice for patients who have bronchiectasis or cystic fibrosis, although evidence suggests that bilateral pneumonectomy and single lung transplantation may be an option in the future. The actuarial survival for cystic fibrosis at 1 year after transplant was 72% and at 4 years 49% (as of January 1997). No survival data are available for other forms of bronchiectasis.

Longevity in patients with bronchiectasis has improved markedly over the past 50 years, owing to the impact of antibiotics. Early in this century, life expectancy for a patient with severe bronchiectasis was no greater than for most untreated malignancies. Since the 1960s, the mean age at death has remained at about 53 years, compared with a death rate of 70% before the age of 40 in a large series published in 1940.

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54. OXYGEN THERAPY

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Oxygen-enriched air is principally used in medicine to treat tissue hypoxia. Tissue oxygenation, however, cannot be measured directly in most clinical circumstances. Clinicians must rely on more accessible measures (e.g., arterial blood oxygenation) that can be measured directly in blood samples (Pa_{O_2} and hemoglobin-oxygen saturation) or estimated in vivo using *pulse oximetry*. Although most pulmonary causes of tissue hypoxia result from arterial hypoxemia, in some cases additional determinants of systemic oxygen transport (i.e., hemoglobin, oxyhemoglobin dissociation, and cardiac output) also must be considered.

Supplemental oxygen may be necessary acutely or chronically in many diseases, including chronic obstructive lung disease (COPD), interstitial lung disease, malignancies, infections, cardiac and noncardiac pulmonary edema, and primary pulmonary hypertension. In carefully selected patients, oxygen can prevent or reverse effects of hypoxia such as dyspnea, effort intolerance, pulmonary hypertension, heart failure, erythrocytosis, and some neuropsychiatric abnormalities.

Several modalities are available for delivery of supplemental oxygen in acute respiratory failure. A patient who is endotracheally intubated or tightly fitted with a mask with straps can be provided a specified fractional concentration of oxygen. All other modes of oxygen delivery enrich the concentration of oxygen in the inspired air but do not allow the patient to receive a constant or precisely specified concentration of oxygen. A number of devices can deliver a specified concentration of oxygen to the vicinity of the patient's airway, but the concentration actually received by the patient depends on the amount of room air inspired with the oxygen. The concentration of oxygen received will vary with the flow of oxygen, the location and fit of the oxygen delivery device, and the patient's minute ventilation, inspiratory flow rate, and tidal volume.

Most patients with a chronic need for oxygen therapy and many patients with acute need can be managed by modest supplementation of the inspired oxygen concentrations. The most common modes of delivery are nasal cannula (up to 6 L/min) or a mask (up to 15 L/min). The flow of oxygen is set empirically, and effectiveness is evaluated using oximetry or arterial blood gas measurements. The patient's oxygen requirements will vary with patient activity and pattern of ventilation, as well as with changes in the disease process.

When patients require chronic oxygen therapy, it may be helpful to improve the efficiency with which a given amount of oxygen is utilized to reduce costs and increase patient mobility. Devices that store small volumes of oxygen in a reservoir at the nose or in a pendant on the chest increase the amount of oxygen provided during inspiration and decrease the waste of oxygen during expiration, allowing the same level of patient oxygen saturation with lower rates of oxygen flow per minute. Also, devices attached to the oxygen source that limit the flow of oxygen to the inspiratory phase of breathing (*pulse* or *demand delivery* devices) can improve the efficiency of gas delivery and extend the life of portable sources.

A chronic transtracheal cannula can also reduce the amount of oxygen needed to sustain adequate saturation. The cannula is inserted percutaneously in the neck directly into the trachea, preferably between the second and third tracheal rings. Some patients prefer this method because it moderates the cosmetic and physical discomfort associated with nasal cannulas. However, patients need to be carefully instructed and meticulous in the care and cleaning of the catheter.

Some oxygen devices are designed so that the flow of oxygen entrains room air to produce a specified concentration of oxygen. These devices are useful for some individuals with COPD who retain carbon dioxide when exposed to high concentrations of oxygen. The masks are labeled as delivering 22%, 24%, or 28% oxygen, and they ensure that the patient will not receive higher than the specified concentration. However, there is no assurance that the patient will not receive a lower concentration, as the gas delivered is often mixed with room air before inhalation. These devices are also available to deliver higher concentrations of oxygen, which occasionally leads to confusion when the physician prescribes a concentration of oxygen with the assumption that the level specified is the lowest level of oxygen received by the patient rather than the level that will not be exceeded.

Patients with acute hypoxic respiratory failure often require high concentrations of oxygen to maintain acceptable levels of arterial oxygenation. A variety of devices have been developed to meet this need, including masks with nonrebreathing bags. More recently, use of gas blenders has allowed delivery of known concentrations of oxygen at flow rates greater than 100 L/min. High concentrations of oxygen in the inspired gas can be sustained at these flow rates, even when the patient is breathing rapidly. This technique maintains better arterial oxygenation in these critically ill patients and reduces their hypoxic ventilatory drive, resulting in less respiratory muscle fatigue. Both factors may reduce the need for endotracheal intubation in this group of patients.

In most patients, tissue hypoxemia is adequate when the oxyhemoglobin saturation (Sa_{O_2}) is maintained at 90% to 92%, typically corresponding to a Pa_{O_2} of at least 60 mm Hg. A major increment in arterial oxygen content can be achieved by raising the Pa_{O_2} up to this level. However, because of the shape of the oxyhemoglobin dissociation curve, as the hemoglobin approaches full saturation further increments in Pa_{O_2} result only in very small increases in arterial oxygen content. In certain clinical situations, such as carbon monoxide poisoning, a higher Pa_{O_2} may restore oxyhemoglobin saturation and promote diffusion of oxygen into ischemic tissue.

Patients with COPD and, in lesser numbers, patients with interstitial lung disease comprise the largest patient groups receiving chronic supplemental oxygen. Several trials of long-term domiciliary oxygen therapy have demonstrated a variety of physiologic and socioeconomic benefits in selected individuals. These benefits include improvements in exercise tolerance, reduction of pulmonary hypertension, improved neuropsychological function, control of erythrocytosis, increased gainful employment, and reduced hospitalization requirements and hospital costs. Prior studies in both England and the United States indicate a reduced mortality rate in hypoxemic patients with COPD receiving long-term oxygen therapy (15–24 h/d).

For chronic therapy, the two most common sources of oxygen are oxygen tanks (liquid oxygen or compressed gas) and oxygen concentrators. Portable oxygen tanks are useful when the patient is away from the home for up to 8 hours at a time, but must be replaced frequently. Liquid oxygen is more condensed and can be carried in smaller, more portable tanks. Gaining popularity are newer devices that deliver oxygen only on patient inspiration, increasing the efficiency of oxygen use and extending the usable life of portable oxygen tanks. Stationary oxygen reservoirs or oxygen concentrators are

used in the home, with variable tubing lengths to allow room-to-room mobility. The oxygen concentrator removes nitrogen from ambient air and delivers oxygen-rich air to the patient. The amount of supplemental oxygen required depends on the severity of the lung disease and on factors such as the patient's level of activity. The amount of oxygen flow needed by a specific patient can be estimated using either Pa_{O_2} or pulse oximetry measurements. Generally, the goal of oxygen therapy is to obtain a Pa_{O_2} of at least 60 mm Hg or a saturation of at least 90%, although the recommendation can differ in specific clinical situations.

The cost of ambulatory oxygen is considerable and long-term therapy should be initiated according to reasonable indications. Oxygen therapy is often initiated after an episode of acute respiratory failure. However, nearly one half of hypoxemic COPD patients initially selected for oxygen therapy (based on low Pa_{O_2}) will improve enough within a few months of outpatient treatment to allow suspension of oxygen use. An initial 1-month stabilization program is recommended, during which time the patient should receive oxygen, but a final decision regarding dose and duration should be postponed. Decisions about the requirement and dose of oxygen should be based on measurements of arterial oxygen levels during rest, exercise, and sleep. Many patients with COPD develop their greatest hypoxemia during sleep. Because most laboratories cannot measure oxygenation during sleep, an increment of 0.5 to 1.0 L/min of oxygen over the daytime requirement is reasonable. No evidence supports the efficacy of oxygen-as-needed programs adopted by some patients, except for the psychological support that unfortunately makes discontinuation difficult. Such difficulties are best avoided by patient education. Explain that the need for supplemental oxygen is not dictated by breathlessness and that, for patients with resting hypoxemia, treatment regimens of less than 12 h/d are of no known benefit. Every 4 to 6 months, re-evaluation of symptoms, signs, and hypoxemia will define the adequacy of treatment and whether changes in therapy are indicated.

In 95% of stable patients with hypoxemic COPD, nasal-prong oxygen at flow rates of 1 to 3 L/min will reverse the resting hypoxemia. If resting flow rates greater than 3 L/min are required, consider whether the patient's condition is unstable, whether the delivery system is faulty, or whether another type of cardiopulmonary disease exists. Evidence supports the conclusion that such flow rates over long periods of time are nontoxic.

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V. ACUTE RESPIRATORY FAILURE

55. ACUTE HYPERCAPNIC RESPIRATORY FAILURE

Timothy A. Morris

The principal function of the lungs is gas exchange; *hypercapnea* indicates severe compromise of this vital function. Although disease can substantially affect any of the functional elements of the respiratory system, the term *acute respiratory failure* is used only when gas exchange is so severely impaired that arterial hypercapnea or hypoxemia occurs. Hypoxemia can involve a multitude of respiratory and metabolic processes and can occur in the absence of hypercapnea. However, hypercapnea is more directly linked to gas exchange insufficiencies, resulting from dysfunction of one or more elements of the respiratory system (e.g., control of breathing, mechanical performance of the lungs, respiratory muscle function, lung parenchyma, and vasculature). Hypercapnic respiratory failure (HRF) nearly always involves some level of hypoxemia and is often referred to as *alveolar hypoventilation*.

Specific values of arterial P_{CO_2} that define HRF are not well defined, but most experts agree that a P_{CO_2} greater than 45 mm Hg (in a previously eucapnic patient) represents acute failure. In patients with chronic hypercapnic lung disease, a sudden increase of 5 mm Hg or more from previously stable levels represents acute respiratory failure superimposed on chronic respiratory failure.

The hallmark of acute HRF is an elevated arterial P_{CO_2}. A rise in P_{aCO_2} signals that the pulmonary *clearance* of carbon dioxide is inadequate; that is, more carbon dioxide is being produced by body metabolism than the respiratory apparatus can clear by ventilation. This relationship is defined by the equation:

$$P_{aCO_2} = K \dot{V}_{CO_2} / \dot{V}_A$$

In this equation, $\dot{V}_{CO_2}$ represents carbon dioxide production; $\dot{V}_A$, alveolar ventilation; and K, a constant. An increase in $\dot{V}_{CO_2}$ is virtually never the primary cause of hypercapnia. Excessive CO_2 formation can occur, for example, when the caloric intake exceeds the daily need; nevertheless, the respiratory system can usually compensate for the higher ventilatory requirement. When other elements of the respiratory system are impaired, however, increases in $\dot{V}_{CO_2}$ can contribute to hypercapnia. Thus, the central cause of HRF remains inadequate alveolar ventilation.

Alveolar ventilation is a physiologic concept described by the equation:

$$\dot{V}_E = \dot{V}_A + \dot{V}_D$$

The volume of gas expired per minute, or *minute ventilation* ($\dot{V}_E$) is a measurable quantity. The equation implies that the minute ventilation is divisible into two separate components: (1) alveolar ventilation ($\dot{V}_A$), which participates in gas exchange, and (2) dead space ventilation ($\dot{V}_D$), which does not participate in gas exchange. $\dot{V}_D$ can also be viewed as *wasted* ventilation, that is, ventilation that does not reach the gas-exchanging areas of the lung. Rearranging this equation,

$$\dot{V}_A = \dot{V}_E - \dot{V}_D$$

This expression of alveolar ventilation makes it clear that hypercapnia occurs via two distinct mechanisms: (1) a reduction in minute ventilation itself (*absolute hypoventilation*), or (2) an increase in dead space ventilation (*relative hypoventilation*).

Although mixed forms do occur, the distinction between absolute and relative hypoventilation is useful in separating HRF into two major categories: those with normal lungs, and those with intrinsic diseases of the lungs. Patients in the first category

manifest hypercapnia because of inadequate minute ventilation caused by abnormalities in respiratory control (induced by disease or drugs), neuromuscular disorders, or chest wall abnormalities. Lung function may be normal in this group. Patients in the second category have lung disease, most commonly emphysema, bronchitis, or asthma. Hypercapnia occurs because of maldistribution of ventilation and perfusion leading to increase in dead space (wasted) ventilation, although alterations in respiratory muscle function and other factors also can play an important role. The net result of these derangements is inadequate carbon dioxide clearance, even though minute ventilation (and respiratory drive) is normal or increased.

Combined forms of HRF occur occasionally, such as in the patient with chronic obstructive pulmonary disease (COPD) who receives sedatives or narcotics for anxiety or sleeplessness, or because of a misdiagnosis of left ventricular failure. Similarly, excessive diuretic use or other circumstances can cause hypokalemia, hypomagnesemia, or hypocalcemia and impair diaphragmatic contractility. Somewhat controversial is the role that absolute and relative hypoventilation play in the acute worsening that patients with chronic hypercapnea may experience when they are treated with excessive amounts of supplemental oxygen (discussed below).

Whatever the pathogenesis of HRF, its consequences are the same. All patients with acute hypercapnia have hypoxemia, acidosis, an increase in pulmonary vascular resistance, and dilatation of the cerebral vessels. Arterial hypoxemia is an inevitable consequence of hypercapnia because, as alveolar P_{CO_2} rises, alveolar P_{O_2} (and therefore arterial P_{O_2}) must fall. If hypercapnia alone is responsible for hypoxemia, the alveolar-arterial oxygen difference ($P[A-a]_{O_2}$) is not widened. If this difference is widened, hypoxemia is more severe, indicating coexistent cardiopulmonary disease. For example, in acute respiratory failure induced purely by drug overdose, hypoxemia is fully explained by hypercapnia and the $P(A-a)_{O_2}$ is normal. If, however, the patient has aspirated and caused zones of acute lung injury, the resulting low ventilation-perfusion ($\dot{V}/\dot{Q}$) zones will make the hypoxemia more severe and the $P(A-a)_{O_2}$ will be increased.

Acidosis is a direct consequence of hypercapnea, although patients with acute respiratory failure may have other reasons for acidosis. The severity of acidosis attributable to hypercapnea itself can be calculated using the equilibrium expression:

$$Ka = [H_2CO_3]/[H^+][HCO^{3-}]$$

Rearranging the terms yields the Henderson-Hasselbalch equation:

$$pH = pKa + \log\left([HCO^{3-}]/[H_2CO_3]\right)$$

or:

$$pH = 6.1 + \log[HCO^{3-}]/0.03 \times PaCO_2$$

If the HCO_3^- concentration were constant (no metabolic acid-base disorder), the Henderson-Hasselbalch equation is approximated (between pH 7.0 and 7.5) by a linear formula:

$$\Delta\, pH = 0.008 \cdot \Delta\, PaCO_2$$

Within these limits, an acute change in $PaCO_2$ of 10 mm Hg will change (in the opposite direction) the blood pH by 0.08. Changes in pH not predicted by this equation must be attributed to other causes besides acute hypercapnea.

Alveolar hypercapnia, hypoxemia, and arteriovenous acidosis all contribute to constriction of the pulmonary resistance vessels. Such constriction increases the pulmonary arterial pressure and, therefore, the work of the right ventricle and can lead to right ventricular failure. Conversely, these same factors cause dilatation of cerebral

resistance vessels. This dilatation leads to an increase in intracranial pressure. Combined with the direct effects of hypoxemia and hypercapnia, this factor explains the disorientation, personality changes, coma, headache, papilledema, and asterixis that can appear in patients with HRF.

The primary goals of management in acute HRF are to (1) prevent respiratory arrest in patients who are rapidly decompensating; (2) restore adequate gas exchange; and (3) treat the disorder(s) responsible for inducing respiratory failure. The goals can be pursued simultaneously.

The development and worsening of hypercapnea strongly suggests that a patient's respiratory system is failing and dangerous degrees of hypoxemia are imminent. Under these circumstances, severe hypoxemia is the greatest danger to patient survival and requires immediate attention. In some cases of mild HRF, supplemental oxygen alone may stabilize the patient. However, oxygen alone may not reverse the respiratory decompensation observed in many cases of severe hypercapnic failure. Furthermore, two potential risks are associated with the administration of high oxygen concentrations to patients with HRF: respiratory depression and worsening of $\dot{V}/\dot{Q}$ mismatching.

The hazard of respiratory depression with oxygen delivery is confined to patients with HRF in whom the normal stimuli to ventilation are compromised and in whom hypercapnia has been present for at least several days. In these patients, retention of bicarbonate leads to moderation of the acidosis that acute hypercapnia causes in both the arterial blood and cerebrospinal fluid—an acidosis that provides a strong drive to respiration. In acute HRF, these drives are present and oxygen poses no depression hazard. In chronic hypercapnic states, however, particularly if the patient is obtunded or sedated, hypoxemia is the major residual drive to ventilation. Oxygen administration can blunt this drive; the patient ventilates less, and the P_{CO_2} rises. Moreover, the P_{aCO_2} can rise even if the $\dot{V}_E$ does not decrease, because of worsened relative hypoventilation. Excessive supplemental oxygen raises the alveolar P_{O_2} in diseased areas of the lung that are not normally well perfused. In these areas, hypoxic vasoconstriction is reversed by the presence of supplemental oxygen and blood flow to them is increased. Increased perfusion to the diseased areas of the lung worsens $\dot{V}/\dot{Q}$ mismatching, leading to an apparent increase in V_D/V_T and worsened hypercapnea. Whatever the mechanisms, the fact remains that excessive oxygen administration to patients with chronic hypercapnea can induce hypercapnic coma and death.

Both excessive oxygen delivery and sedatives should be avoided in patients with chronic hypercapnia. Although oxygen therapy to relieve hypoxemia is essential in any patient with HRF, it should be used judiciously in those with chronic hypercapnea. A reasonable goal of oxygen therapy in these patients is to establish a P_{O_2} in the 50 to 60 mm Hg range, corresponding to an oxygen saturation of approximately 90%. In these cases, it is imperative to closely monitor the arterial P_{O_2} and P_{CO_2} during therapy with oxygen.

If supplemental oxygen fails to provide an adequate P_{O_2} without inducing marked hypercapnia, or if clinical signs of respiratory decompensation are detected, the next step is use of a mechanical ventilator. This step is a major decision because it generally requires endotracheal intubation; it may require sedation or paralysis and makes patients totally dependent on a *closed system* and the personnel caring for them. Furthermore, this step exposes patients to new risks. Therefore, the decision to initiate mechanical ventilation should not be made until it is clear that simpler measures will not suffice. Despite intensive investigative efforts, no absolute criteria for intubation-ventilation exist. The decision still rests on an overall assessment of the individual patient, particularly the degree of hypoxemia and acidosis and, often, the response to a trial of nonventilator management.

A potential intermediate step can be taken before intubation-ventilation, namely, the use of various nasal or nasal-oral continuous positive airway pressure devices. Some centers have reported success in selected patients using mechanical ventilation through face masks—without controlling the airways with endotracheal tubes. Defining how often and in which patients such approaches will suffice remains an investigative challenge.

Gas exchange aberrations pose an immediate risk to patient survival, and should be corrected. Prompt action must be taken to reverse or avoid hazardous levels of hypoxemia, hypercapnia, and acidosis. Such levels must be defined rather arbitrarily, because

coexistent conditions modify such definitions. For example, a degree of hypoxemia well tolerated by a young adult with a barbiturate overdose may be hazardous in a person who has recently sustained a myocardial infarction. Reasonable agreement is seen, however, that P_{O_2} levels below 40 mm Hg are poorly tolerated by adults; these levels are commonly associated with cardiac arrhythmias and functional or anatomic abnormalities of the heart, brain, kidney, liver, and other organs. The dangerous effects of P_{CO_2} relate chiefly to the degree of associated acidosis. Thus, a chronically elevated P_{CO_2} of 60 mm Hg with an essentially normal pH is not dangerous, whereas a sudden rise to 60 mm Hg induces a potentially hazardous acidosis. In the nonintubated patient, a blood pH below 7.2 indicates imminent respiratory arrest and available data indicate that the mortality risk rises with each decrement below 7.2. Once the risk of respiratory arrest has been minimized by intubation and mechanical ventilation, however, the levels at which hypercapnea and respiratory acidosis become harmful are more difficult to establish. Whereas acidosis itself potentiates the functional abnormalities induced by hypoxemia (e.g., pulmonary hypertension, cerebral vasodilatation, and depression of myocardial contractility), no *hazardous* level is widely accepted. Indeed, excessive attempts to lower arterial P_{CO_2} in mechanically ventilated patients, by increasing minute ventilation at the cost of alveolar overdistention and lung damage, are probably misguided. To spare the lungs from trauma during mechanical ventilation, some experts use lower tidal volumes and respiratory rates, allowing the P_{CO_2} to rise to high (previously considered alarming!) levels. Within limits, this strategy of *permissive hypercapnea* is well tolerated by respiratory failure patients, provided that adequate blood oxygenation is ensured.

As the life-threatening alterations in gas exchange are being controlled, attention must also be directed toward diagnosis and treatment of the disorder(s) that induced HRF. In some instances, diagnosis of the precipitating disorder may determine decisions regarding institution of mechanical ventilation.

In patients with absolute hypoventilation (reduced $\dot{V}_E$), the primary problem is usually readily identified and treated. For example, respiratory depression caused by drug overdose can be treated with specific antagonists or by enhancing drug excretion using dialysis. Myasthenia gravis or myxedema can be treated with specific agents. In patients with the Guillain-Barré syndrome, however, ventilatory support is required until the disorder runs its course.

Among patients with relative hypoventilation caused by obstructive lung disease, therapy is directed toward the problems that caused acute deterioration in gas exchange. The most frequent reversible problems are accumulation of secretions, infection, and bronchospasm. As these abnormalities are resolved, the mechanical function of the lungs improves, $\dot{V}/\dot{Q}$ relationships return toward normal, and gas exchange is enhanced. In some patients, recovery depends on these factors alone. In others, the respiratory muscles may have become exhausted from hours or days of respiratory failure and mechanical ventilation may be necessary until they have adequately rested.

Secretions are best removed by encouraging the patient to cough and by adequately hydrating the patient. Little evidence indicates that available *mucolytic* agents are of significant value. However, new agents with greater potency (e.g., deoxyribonuclease) need evaluation in this context. Hydration is best achieved by oral fluid intake; if this intake is not adequate, intravenous administration or aerosolization of water or both can be added. Sputum mobilization can be enhanced by chest percussion and vibration and by instruction from a skilled respiratory or physical therapist. If necessary, catheters inserted by the nasal or oral route into the trachea can be used to suction secretions, or fiberoptic bronchoscopy can be performed.

The treatment of bronchospasm is an integral part of the management of most patients with HRF associated with COPD because most patients have some degree of reversible bronchoconstriction (see Chapters 47 and 51).

Infection is a frequent cause and a common complication of HRF in patients with COPD and other chronic lung diseases. Treatment with broad-spectrum antimicrobial drugs (ampicillin, tetracycline, trimethoprim-sulfamethoxazole, ciprofloxacin, and others) should be initiated on the presumption that infection is present. However, appropriate samples for smear and culture should be requested so that more specific therapy can be applied, if indicated.

Corticosteroids are commonly given during the first few days of therapy, usually in high doses to reverse airway inflammation and bronchospasm. Large clinical trials comparing different doses are unavailable. Most clinicians initiate therapy with the equivalent of 100 to 125 mg of methylprednisolone on presentation, followed by about one half this dose every 6 hours. Empiric trials suggest that such therapy has a modest positive impact on the course of patients with HRF.

It is important to consider and search for other factors that may have induced HRF, particularly left ventricular failure and pulmonary embolism, and to pay attention to the patient's nutritional needs. Left ventricular failure can cause $\dot{V}/\dot{Q}$ aberrations because of alveolar edema as well as dysfunction of poorly perfused respiratory muscles. Cardiac ischemia is increasingly recognized as a reason for failure of some patients to *wean* from mechanical ventilation. Pulmonary embolism is common in patients with acute and chronic lung disease. In most patients who die with pulmonary embolism, clinicians had not suspected the diagnosis premortem—possibly because the characteristic signs and symptoms were attributed to other coexisting lung conditions (see Chapter 63). Many patients with COPD are malnourished; correction of nutritional depletion and avoidance of further depletion during a bout of ARF, may enhance recovery and forestall future episodes of ARF (see Chapter 60).

The role of respiratory muscle performance and respiratory control in the pathogenesis of HRF has generated a great deal of research interest. Treatment for alterations of respiratory control is not yet available, but respiratory muscle performance can be improved by several proposed methods. Putting the respiratory muscles to rest can improve muscle performance in some patients with acute respiratory failure. Some patients have chronic respiratory muscle dysfunction and may benefit from pharmacologic therapy. Some physicians have advocated the use of theophylline preparations in this setting because these agents are known to modestly enhance diaphragmatic function.

Patients with HRF are subject to complications associated with both respiratory failure and its treatment. Often such complications lead to acute deterioration in a previously stable or improving patient. Several common complications have been identified: *Cardiac arrhythmias* of all types are common, relating to diverse factors including hypoxemia, wide swings in pH, electrolyte disturbances, and drugs that may be used (e.g., β-adrenergic agents, theophylline, and digoxin). *Gastrointestinal hemorrhage*, chiefly from the stomach and duodenum, is frequent. Again, multiple factors may be involved, and the hemorrhage can be sudden and massive. *Pneumothorax* occurs in a significant number of patients with respiratory failure, particularly among those who are mechanically ventilated. *Bronchial obstruction* can occur because of thick, inspissated secretions or improper placement or obstruction of endotracheal tubes. Other complications include acute right or left ventricular failure (or both), pulmonary embolism, and convulsions caused by hypoxia or even by alkalosis following sudden reversion of hypercapnia.

The patient with HRF requires a careful initial evaluation and close monitoring throughout management. Such patients are best cared for in a respiratory intensive care unit staffed by experienced personnel and properly equipped. In this environment, most patients can be stabilized promptly, decisions regarding the need to intubate and mechanically ventilate can be made properly, and therapy can be applied and monitored appropriately.

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56. THE ACUTE RESPIRATORY DISTRESS SYNDROME

Robert M. Smith

A marked increase in the permeability of the alveolar-capillary membrane to water, solutes, and plasma proteins is the defining characteristic of the acute respiratory distress syndrome (ARDS). The 1972 National Heart, Lung, and Blood Institute Task Force on Respiratory Diseases estimated that approximately 70 cases of ARDS occur annually in the United States per 100,000 population. Although some evidence suggests that the incidence has decreased somewhat in the last decade, ARDS remains a frequent and dreaded problem in modern intensive care units. Events that have preceded and appear to act as precipitants to ARDS are remarkably diverse (Table 56.1), although sepsis and trauma are the most commonly associated clinical settings. The wisdom of grouping patients with such disparate precipitating factors under the umbrella of ARDS has frequently been debated. However, as the biochemical and cellular pathways that lead to ARDS are not understood and as the patients have a number of apparent physiologic and histologic features in common, it has proved useful to consider them together. The probability of developing ARDS increases with multiple risk factors, but it is not known whether different precipitants act independently or via some common pathway leading to lung injury.

No specific physical or laboratory findings exist for the diagnosis of ARDS. Before the development of frank respiratory failure, respirations are rapid and shallow, and the patient may be cyanotic. Auscultation usually reveals bronchial breath sounds; rales are often not heard. Serum chemistries and blood cell counts tend to reflect the presence of underlying diseases. Arterial blood gas analyses typically show markedly reduced Pa_{O_2} with a normal or reduced Pa_{CO_2}; when the fully developed syndrome is present, the Pa_{O_2}:F_{IO_2} ratio is typically less than 200 mm Hg. The chest roentgenogram shows rapidly progressing diffuse infiltrates, often with characteristics suggesting alveolar filling. Occasionally is seen a brief early period during which an interstitial infiltrate predominates. Particularly in the early stages, the infiltrates may look patchy or appear to spare some parts of the lung, leading to a mistaken diagnosis of pneumonia.

Clinically, physiologically, and pathologically, ARDS typically progresses through successive stages. After exposure to one of the triggering events noted above, often an interval of apparently normal lung function occurs, which can last hours to days. With the onset of symptoms, there is rapidly worsening gas exchange with decreasing lung compliance and functional residual capacity over 1 to 3 days. Subsequently, lung compliance decreases further, and increases occur in V_D/V_T and pulmonary vascular resistance. Multiple organ system failure often becomes apparent at this point, although it

Table 56.1. Clinical settings associated with the development of ARDS

ARDS Occurs in More Than 1% of Patients at Risk
–Aspiration of gastric contents
–Pneumonia requiring intensive care unit admission
–Severe sepsis
–Multiple trauma
–Disseminated intravascular coagulation (usually associated with other events)
Cases in Which ARDS is Reported
–Near drowning
–Smoke inhalation
–Inhalation of irritant or toxic gases
–Fat or air embolism
–Pancreatitis
–Hypertransfusion
–Thermal burn
–Cardiopulmonary bypass
–Narcotic administration

ARDS, acute respiratory distress syndrome.

can occur at any time. Renal dysfunction, hepatic dysfunction, and biventricular cardiac dysfunction may be seen. It is not known whether impairment in these organ systems is caused by the same process precipitating ARDS (e.g., sepsis) or to distinct pathologic processes. In addition, the interventions used to support gas exchange (e.g., mechanical ventilation or positive end-expiratory pressure [PEEP]) can also have deleterious effects on organ function. Finally, from 10 to 30 days after the onset of symptoms, the patient may enter a more chronic stage in which pulmonary function has stabilized, although persistent functional impairment remains. If the patient survives to enter this latter stage, usually lung function gradually improves over weeks to months, and mortality more often results from nonpulmonary causes.

Histologic examination of pulmonary tissue also suggests the presence of acute and chronic stages of ARDS. In the early stages, termed the *exudative phase*, the alveolar type I epithelial cells are focally destroyed and endothelial cells may appear swollen. Neutrophils are seen clogging capillaries and extravasating into the interstitium. Interstitial edema is found, with cuffs of edema around bronchioles and vessels. The alveoli are filled with proteinaceous exudate containing red blood cells, neutrophils, macrophages, and cell fragments. Increased numbers of cells are recovered in bronchoalveolar lavage fluid, and polymorphonuclear neutrophil leukocytes; normally < 2% (of recovered cells) predominate. A more chronic stage of acute lung injury, termed the *fibroproliferative phase*, is apparent after 1 to 2 weeks. Plasma cells, histiocytes, and lymphocytes are seen in the interstitium and are accompanied by proliferation of pericytes and fibroblasts. Intravascular microthrombi are common. Cuboidal epithelial cells cover the surfaces of alveoli and alveolar ducts, and the acinar architecture of the lung is progressively replaced by thick bands of fibrotic tissue.

The processes responsible for tissue injury in ARDS remain obscure. Neutrophils and their granular products have been implicated in the pathogenesis of ARDS in animal models, and evidence of neutrophil granule release (e.g., the presence of elastase or myeloperoxidase) is often found in lung lavage fluid. Similarly, the production of highly reactive oxygen radical species by neutrophils or by resident lung macrophages may contribute to ARDS, either by direct tissue injury or by modification of proteins, lipids, or DNA, which leads to inactivation (e.g., α_1-proteinase inhibitor) or abnormal function. A number of factors can lead to neutrophil accumulation in the lung. Cytokines, elaborated systemically or locally in the lung following sepsis or trauma, can act as chemotactic factors (e.g., interleukin-8) or can cause upregulation of endothelial and leukocyte adhesion molecules (e.g., interleukin-1). In preliminary studies, an elevated level

of IL-8 in alveolar lavage fluid of patients at risk for ARDS predicts the subsequent development of the full-blown syndrome. However, this finding has not been confirmed in larger studies and the complex interplay between the various cytokines is not yet well understood. The occurrence of ARDS in severely neutropenic patients and the lack of neutrophil participation in some animal models of ARDS suggest that neutrophil-independent mechanisms of tissue injury are also important. Loss of surfactant activity in lung lavage is seen early in ARDS and is a potential explanation for many of the physiologic abnormalities. The loss of surfactant activity is caused, in part, by alterations in surfactant production by type II pneumocytes and, in part, by inhibition of surfactant activity by the ingress of plasma proteins.

One novel mechanism for lung injury stems from the observation that the application of positive pressure ventilation in animal models results in diffuse lung injury with histologic features indistinguishable from those of patients with ARDS. This injury occurs in animals with even modest levels of positive pressure (e.g., sustained peak airway pressures of 30 cm H_2O for 24 hours). Data suggest that injury may be caused by cyclic opening and closing of alveoli or by overdistention and stretching of the alveolar capillary membrane at peak inflation. Injury is diminished in these models by limiting maximal ventilatory excursion or by the application of PEEP. Further studies have demonstrated the elaboration of proinflammatory cytokines and the alteration of surfactant structure and function in the lungs of these animals as a result of positive pressure ventilation. Although these studies do not shed light on the pathophysiologic events initiating ARDS, they do support the hypothesis that the ventilatory support necessary to preserve gas exchange can worsen or modify the course of the underlying lung injury.

Initial management of the patient with ARDS centers on supporting the patient while identifying and treating potentially reversible processes that can exacerbate or mimic ARDS. An aggressive diagnostic approach is warranted in the patient with known or suspected immunocompromise. In particular, bronchoscopy with lavage and brushings may be useful to determine the presence of *Pneumocystis carinii* pneumonia for patients suspected of having the acquired immunodeficiency syndrome. Transbronchial biopsy may be considered, but the risk of complications in the setting of mechanical ventilation suggests this approach should be used with caution. Open lung biopsy should be considered for those patients in whom no specific diagnosis can be made with less invasive techniques.

Oxygenation of the arterial blood and delivery of that oxygen to peripheral tissues are the primary goals of supportive therapy in ARDS. Those goals must be coupled with limiting further lung injury that could be caused by ventilatory support. Initially, supplemental oxygen supplied with face mask or nasal cannula may be adequate. However, tracheal intubation and positive pressure ventilation are usually needed and should be instituted as soon as it is apparent that an acceptable Pa_{O_2} cannot be maintained with supplemental oxygen alone. The optimal method of supplying ventilatory support remains controversial. However, as in animal models of lung injury, a recent National Institutes of Health-sponsored trial of low stretch ventilation (low tidal volume) compared with high stretch ventilation (high tidal volume) demonstrated a marked reduction in ARDS mortality when the low stretch *lung-protective* strategy was followed. In this study, patients ventilated with 6 ml/kg tidal volumes had a 30% mortality rate compared with a 40% mortality rate experienced in patients subjected to *standard* 12 ml/kg tidal volume ventilation. Although this study used a volume-controlled method of mechanical ventilation, end-inspiratory plateau pressures were limited to 25 cm H_2O and 45 cm H_2O in the low- and high-stretch arms, respectively. It is likely that other ventilatory strategies that limit end-inspiratory pressure to a similar level of 25 cm H_2O (e.g., pressure-cycled ventilation) would be equally successful.

At levels from 10 to 15 cm H_2O, PEEP should be applied when positive pressure ventilation cannot maintain a Pa_{O_2} greater than 55 to 60 mm Hg using an F_{IO_2} of 0.6 or less. The physiologic effects of PEEP are thought to result from (1) redistribution of capillary blood flow, resulting in improved $\dot{V}/\dot{Q}$ matching; and (2) the recruitment of previously collapsed alveoli and prevention of their collapse during exhalation. The net effect of these changes is an improvement in Pa_{O_2}, which then allows a reduction in F_{IO_2}. The improvement in lung function because of PEEP may require 30 to 60 minutes

to become apparent but is lost at a more rapid rate if PEEP is removed. PEEP also can have significant deleterious consequences. As end-expiratory pressure is increased, mean thoracic pressure can also increase and compromise venous return. In addition, PEEP can directly affect cardiac function by restricting the filling of the atria or ventricles during diastole. On the plus side, the application of PEEP appears to limit alveolar excursion during positive pressure ventilation and protects from ventilation-associated lung injury in animal models. Although PEEP is useful for the support of patients at nontoxic FIO_2, early *prophylactic PEEP* has been shown ineffective in preventing subsequent ARDS.

It is vital to recognize and to balance the beneficial and deleterious effects of ventilatory support techniques. Improvements in PaO_2 brought about by the incremental application of PEEP must be weighed against any decrement in cardiac output and the resulting drop in oxygen delivery. To achieve this balance, it is important to monitor the variables that determine cardiac function (pulmonary artery and pulmonary artery wedge pressures), as well as those that measure total arterial oxygen delivery (arterial oxygen saturation, hemoglobin, and cardiac output). Measurements of the mixed venous oxygen tension (PvO_2) and the difference between arterial and mixed venous oxygen contents ($C[a\text{-}v]O_2$) have also been suggested as useful monitoring techniques. In those patients with hemodynamic instability, it is advisable to use a pulmonary artery catheter with cardiac output monitoring capability to assess the effectiveness of fluid administration or the use of inotropic agents. Absolute standards to guide therapy should be avoided. The optimal level of PEEP is usually the lowest level allowing a PaO_2 greater than 55 to 60 mm Hg with an acceptable cardiac output. Further increases of PEEP may improve PaO_2 but can significantly increase the risk of barotraumatic injury and impaired cardiac function.

Alternative methods of ventilatory support have been explored with only limited success and none have demonstrated efficacy in controlled trials. However, high-frequency jet ventilation and high-frequency oscillation coupled with positive pressure ventilation can improve gas exchange in certain patients. Similarly, the use of pressure-cycled inverse ratio ventilation (i.e., inspiratory time greater than expiratory time) can occasionally provide benefit, as can ventilation of patients in the prone position. Although extracorporeal bypass with membrane oxygenation did not improve survival in a large randomized trial, its application in selected patients or the application of extracorporeal carbon dioxide removal through a veno-venous bypass circuit may preserve function where other approaches fail. Inhalation of nitric oxide improves PaO_2 acutely, but has not had a measurable impact on survival in a number of well-controlled trials.

Ongoing management of the patient with ARDS requires meticulous attention to detail and careful surveillance for possible complications. As for any critically ill patient, appropriate early attention must be paid both to nutritional support and to prevention of venous thrombosis. For patients with severely compromised lung function, sedation and muscle paralysis may be required to prevent struggling against the ventilator and increased oxygen utilization. Any sudden deterioration in hemodynamic status, increase in peak airway pressure, or drop in PaO_2 should suggest the possibility of a tension pneumothorax and prompt immediate action. Daily chest films and frequent examination of the chest for asymmetric breath sounds should be done to survey for slowly developing air leaks. In selected patients, pharmacologic agents (e.g., inotropic agents, vasodilators, or both) may be useful if cardiac output cannot be preserved with acceptable low left ventricular filling pressures. However, optimal management of cardiac function is also an area of ongoing debate. The potential need to maximize filling pressures to prevent a drop in cardiac output with PEEP conflicts with the concurrent need to reduce filling pressures to decrease the leak of fluid across the alveolar-capillary membrane. In general, strategies that aim at reducing lung edema by limiting filling pressures appear more successful. No survival advantage appears to be conferred by elevating cardiac output and tissue oxygen delivery to supranormal levels.

The mortality rate for patients who develop moderate or severe ARDS remains distressingly high (30% to 40%), although this figure represents an improvement over the 90% mortality rate reported in the initial studies of ARDS. In general, mortality in ARDS correlates more with the presence of multiple organ failure and with other coexisting or pre-existing disease than with the severity of pulmonary impairment.

Long-term outlook for survivors of ARDS is relatively good despite the severe physiologic impairment and pathologic changes present during or immediately following hospitalization. Lung volume and compliance often return to predicted levels within 6 to 18 months, and often exercise capacity is only minimally impaired compared with premorbid levels. However, dyspnea persisting months after recovery should prompt a search for causes other than residual fibrosis from ARDS (e.g., tracheal stenosis). Patients with the most severe derangement of function during their acute illness are more likely to have persistent derangement of pulmonary function and have a persistent decrease in health-related quality of life.

Specific therapy for ARDS is not yet available. Early corticosteroid therapy does not prevent the development of ARDS or alter its outcome. Corticosteroid use during the fibroproliferative phase of ARDS can hasten recovery, but their use has not been studied extensively. Efforts to examine the use of agents to block elements of the inflammatory cascade (e.g., cyclooxygenase inhibitors or protease inhibitors) or attempts to manipulate cytokine cascades (e.g., antitumor necrosis factor or interleukin-1 receptor antagonists) have been disappointing. Manipulation of dietary lipids or administration of glutathione precursors may be useful, and instillation of surfactant into the airways early in ARDS appears to improve gas exchange and may reduce overall mortality. In contrast, delivery of surfactant as an aerosol has been unsuccessful, possibly because of the inefficient delivery method. Unfortunately, until recently even research into the use of surfactant in ARDS has been restricted by the limited availability of quantities of surfactant sufficient to treat adult patients. Synthetic surfactant preparations have now been developed and are under investigation.

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57. AIRWAY MANAGEMENT

Robert M. Jasmer

Placement of an endotracheal tube can be a lifesaving procedure in a variety of clinical circumstances. The indications for tracheal intubation are varied and determined by both clinical and laboratory data. The need for mechanical ventilation is the primary indication for tracheal intubation. Another indication is for the relief of upper airway obstruction.

During a respiratory arrest, the airway needs to be controlled immediately. It is critical to open the airway by the head tilt-chin lift maneuver to prevent the tongue from collapsing against the posterior pharynx. Ventilation can be temporarily accomplished using approved techniques of mask-to-mouth resuscitation. At some point, an artificial airway needs to be established. Placement of an oral or nasal endotracheal tube under laryngoscopic or bronchoscopic guidance is the technique of choice in this circumstance. The esophageal obturator is another device useful for establishing an airway in an emergency situation. It permits pulmonary insufflation because the esophagus is occluded (thus permitting the air that ventilates a tight-fitting mask access only to the trachea). Regurgitation of stomach contents is also prevented. Placement of the obturator requires less skill than endotracheal intubation; however, it must be replaced with an endotracheal tube if mechanical ventilation becomes necessary.

In the less acute setting, tracheal intubation may become necessary as ventilation or oxygenation is progressively compromised. Acute upper airway obstruction may also require tracheal intubation or emergency tracheotomy. If the obstruction is caused by aspiration of a large piece of solid matter (the *cafe coronary* syndrome), an attempt should be made to remove the particulate matter manually, followed by forceful compression of the thoracic cage (Heimlich maneuver) in an attempt to dislodge the obstruction. Obstruction of the upper airway caused by infection (acute epiglottis), edema (burn injury, infection, or tumor), or stricture (prior endotracheal intubation) may require endotracheal intubation or emergency tracheotomy.

Endotracheal intubation can be accomplished with an orotracheal tube, a nasotracheal tube, or a tracheostomy tube—each of which has its particular advantages and disadvantages. The orotracheal tube is easily placed in most patients. Passage through the mouth places less limitation on tube size; however, it is uncomfortable for the conscious patient and does not allow oral ingestion of food. Placement of a nasotracheal tube requires somewhat greater skill; however, it can often be done in patients with limited neck mobility, in whom passage of an orotracheal tube is difficult or impossible. If time permits, local anesthesia applied at the nose, nasopharynx, and mouth

reduces patient discomfort and facilitates cooperation. The availability of an endotracheal tube with a guided flexible tip makes it possible to blindly intubate most patients nasotracheally. Nasotracheal tubes have the disadvantages of (1) occasionally kinking in the posterior nasopharynx; (2) more difficulty in suctioning because of their smaller diameters; (3) occluding sinus drainage, thus increasing the risk of sinusitis; and (4) occasionally being uncomfortable for the alert patient. In addition, the size of the nasopharynx can limit the diameter of the tube that can be placed.

In difficult cases, fiberoptic bronchoscopy may be useful in intubating patients, particularly those with arthritic or traumatic neck disorders. In awake patients, administration of intravenous medications for sedation and muscular paralysis can facilitate tracheal intubation and decrease the risk of aspiration. The application of pressure to the cricoid cartilage (Sellick maneuver) during laryngoscopy and intubation helps to occlude the esophagus and prevent potential aspiration. Correct placement of an endotracheal tube leaves the tip 2 to 4 cm above the carina; a chest radiograph should be obtained after intubation to confirm placement. Tube position can also be confirmed by direct visualization of the tube passing through the vocal cords or by bronchoscopy.

A tracheostomy tube placed through a surgically prepared tracheostomy site or through progressive percutaneous dilatation at the cricothyroid or tracheal level is generally well tolerated and allows excellent suctioning capability. Because a tracheostomy tube does not traverse the larynx, vocal cord injury is minimized. Verbalization can occur during spontaneous breathing through a fenestrated tracheostomy tube with a special one-way valve. During positive pressure ventilation, some tracheostomy tubes allow flow of an air jet through the vocal cords and, thus, permit speech, even during mechanical ventilation. Tracheostomy tubes have the obvious disadvantage of requiring a surgical procedure.

Adult nasotracheal, orotracheal, and tracheostomy tubes use an inflatable cuff to seal the tube within the trachea. A common misconception is that this cuff *seal* prevents significant aspiration of oropharyngeal contents. In fact, the cuff provides only partial protection against aspiration; oropharyngeal suctioning still is necessary as well as meticulous attention to cuff inflation, not only to try to prevent aspiration, but also to minimize the pressure being transmitted to the tracheal mucosal surface. The high-volume, high-compliance cuffs can seal the trachea with *minimal leak* and low pressures (<25 mm Hg), which results in significantly fewer cuff-related postextubation tracheal problems because tracheal mucosal blood flow is not compromised.

The routine care of patients with tracheal intubation includes frequent suctioning to prevent accumulation of pulmonary secretions, careful nasal and oral hygiene (including suctioning of oropharyngeal contents), and regular monitoring of cuff inflation pressure. Although the same care is given to patients with tracheostomy tubes in place, attention must also be directed to the surgical incision, with appropriate topical treatment, dressing changes, and avoidance of pressure necrosis at the surgical site.

Patients who are being mechanically ventilated are at risk for potentially catastrophic events that can occur suddenly and which can be related to the underlying disorder or malfunction of the ventilator or artificial airway. If a patient cannot be ventilated, the first step is to disconnect the patient from the ventilator and begin hand ventilation with an anesthesia bag containing 100% oxygen. The artificial airway should be checked for evidence of external obstruction (e.g., kinking of tubing) and for patency by passing a suction catheter through the tube to remove mucus plugs or blood clots that may be causing the problem. If the suction catheter can be passed through the endotracheal tube and into the chest but ventilation is still difficult, potential causes of the difficulty include major airway obstruction not removed by suctioning, peripheral airways obstruction, or pneumothorax. Physical examination is often useful to distinguish among these possibilities—main bronchial obstruction is indicated by the absence of air entry into the lung distal to the obstruction, causing absent breath sounds and dullness to percussion on the affected side; peripheral airways obstruction is often associated with wheezing; and pneumothorax leads to absent breath sounds and hyperresonance to percussion on the affected side. In an emergency setting, a 14-gauge needle can be inserted into the second anterior intercostal space to restore ventilation and blood pressure in a patient with a tension pneumothorax.

The long-term clinically significant complications of endotracheal intubation are less common today than several decades ago because of the softer, more compliant cuffs now

available. Approximately 5% to 8% of extubated patients develop stridor secondary to laryngeal edema, which requires a combination of vasoconstrictors (inhaled racemic epinephrine), anti-inflammatory agents (steroids), or reintubation. Tracheostomy will avoid these laryngeal complications but it is associated with its own, often more serious complications (hemorrhage, barotrauma, and tracheal stenosis, especially at the stomal site). A unique complication of nasotracheal intubation is sinusitis, which has been radiographically detected in approximately 50% of patients after prolonged use.

Clinically, the overwhelming majority of patients who have survived prolonged intubation (up to 3 weeks) recover upper airway function completely. No absolute time limit has been set for endotracheal intubation beyond which tracheostomy is necessary. Tracheostomy can help in weaning the patient from mechanical ventilator support by allowing improved mobilization and better suctioning of airway secretions and by promoting easier communication and swallowing. Therefore, if more than 7 to 14 days of intubation is anticipated in a patient who is expected to survive an acute illness (e.g., spinal cord injury), then a tracheostomy after only a few days of mechanical ventilation may minimize the laryngeal complications associated with transglottic intubation. However, if successful extubation is anticipated within 1 to 2 weeks and the patient is tolerating transglottic intubation well, it is prudent to avoid a tracheostomy. Similarly, performing a tracheostomy on a patient who is so critically ill that survival is not expected serves no useful purpose for the patient. If such a patient does survive, the risk of intubation-related complications is sufficiently small that delaying a tracheostomy until the patient shows signs of improvement is justified.

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58. MECHANICAL VENTILATION: DEVICES AND METHODS

Timothy A. Morris and David M. Burns

The introduction of microprocessor-controlled algorithms to manage and monitor ventilator performance has dramatically expanded the potential for a single ventilator to provide multiple patterns of ventilatory support. Ventilators can cycle from inspiration to expiration based on a set pressure, time, inspiratory flow rate, or tidal volume. A variety of inspiratory flow patterns can be delivered, or inspiratory flow can be adjusted based on the pressure during inspiration. The ratio of inspiratory to expiratory time can be inverted to produce very long inspiratory times, very short expiratory times, or both. Positive end-expiratory pressure (PEEP) can be added at the airway opening to keep alveoli open throughout exhalation. The choice of appropriate modalities for ventilatory support is determined by the respiratory care objectives for the patient at a given point in the disease course (e.g., improved oxygenation, respiratory muscle rest, weaning). One of the advantages of the newer generation of microprocessor-based mechanical ventilators is that it is possible to dramatically change the way that ventilatory support is provided as the patient's needs change, without changing the ventilator.

The wide variety of ventilatory modalities available can be categorized according to how the following functions are performed: (1) control and adjustment of air movement

into the lungs during inspiration; (2) function during exhalation; (3) scheduling of mandatory (machine-driven) breaths; and (4) function during spontaneous (patient-driven) breaths. Each function has the goal of improving arterial oxygenation, protecting the alveoli from overdistention, or reducing the work of breathing by synchronization with spontaneous patient effort.

The fundamental aspect of mechanical ventilation is how air movement into the lungs is controlled and adjusted during inspiration. The basic choice is to control either pressure or flow. The most straightforward model of controlling pressure is a simple pressure-driven system. In this idealized situation, the patient's airway would be connected to a large tank of air maintained at a specific pressure. At the start of inspiration, the pressurized air from the tank would enter the lungs at a flow rate determined by the resistance and compliance of the respiratory system. As the lung pressure approached equilibrium with the air in the tank, flow would decelerate at a rate similarly determined by respiratory resistance and compliance. In this model, the pressure in the airways would be *controlled* at a constant level, while, at any given instant, the flow rate would depend on the resistance and compliance of the respiratory system.

A different idealized model of mechanical ventilation would supply a constant flow of air to the lungs, allowing the pressure to change, depending on the resistance and compliance of the lungs. A simple, idealized model of flow control might involve a highly pressurized tank of air connected to the patient's airway by a resistant valve used to control airflow: a setup similar to the high-pressure pump used to inflate automobile tires at a filling station. In this idealized system, flow is held constant, while the intrapulmonary pressure at any given instant depends on the resistance and compliance of the lungs. The lungs (as the tires) are not allowed to reach equilibrium with the high-pressure tanks. The volume of air delivered to the lungs is determined by the flow rate and duration of the breath delivered.

These two idealized systems are, of course, too cumbersome and inflexible for actual clinical use. However, modern ventilator modalities simulate either one of these two basic models by using microprocessor-controlled valves to regulate the output from high-pressure solenoid pumps. The ventilator generates a *volume controlled* breath by repetitively sampling the flow it is delivering during inspiration, and adjusting the solenoid output to provide a precise flow pattern for a specific duration of time (volume = flow × time). To generate a *pressure controlled* breath, the microprocessor samples the pressure it is delivering and adjusts the solenoid pump output to achieve and maintain a constant pressure in the airways.

Modern ventilators with faster methods of monitoring and adjusting their output, and with more complete control over airway pressure and flow, have increased their versatility and applicability to a variety of clinical needs. For example, if a patient who coughs or *bucks* when an older style ventilator is delivering an inhaled breath (in pressure-control or volume-control mode), the airway pressure can rise rapidly, exposing the lungs to barotrauma before the ventilator detects the high pressure and ends the breath. Modern ventilators, however, can adapt to rapid changes in lung compliance (e.g., coughing or *bucking*) by (1) increasing the rapidity with which the flow and pressure in the airway is monitored; and (2) using the microprocessor to constantly adjust both inhalation and exhalation valves in the airway circuit without ending the inspired breath. Thus, barotrauma is minimized, minute ventilation is preserved, and the work of breathing is reduced.

Modern ventilators can also vary the duration of the inspiratory and expiratory phases of breathing to suit the needs of the patient. Conscious patients, for example, tolerate mechanical ventilation more readily with relatively brief inhalation times, allowing more time for exhalation (similar to the normal cadence of spontaneous breathing). If severe hypoxemia occurs, however, the patient may require long inspiratory and short expiratory times—a reversal of the normal inspiratory-to-expiratory (I:E) time ratio, which is termed *inverse ratio ventilation* (IRV). The IRV mode is commonly used with pressure-controlled ventilation, but can be used with volume control as well. The inspiratory time, respiratory rate, and I:E ratio, of course, are interdependent. Some ventilators allow the user to set two of the parameters (such as I:E and rate) directly; the other parameter is adjusted as needed. Because IRV so distorts the normal pattern of ventilation, the patient usually requires sedation, neuromuscular blockade, or both to avoid patient-ventilator asynchrony. This mode of ventilation is able to achieve

acceptable levels of arterial oxygenation at lower peak and end-expiratory airway pressure. It remains controversial whether this effect is the result of the inspiratory pressure plateau preventing alveolar collapse or whether the short expiratory times, which do not allow expiration flow to finish before inspiration begins, simply provide PEEP at the alveolar level that is not measured at the airway opening (alveolar or intrinsic PEEP).

During exhalation, the ventilator either allows the lungs to reach atmospheric pressure or provides positive pressure throughout exhalation (PEEP). The most common use of PEEP is to prevent damaged alveoli from collapsing during exhalation, increasing the proportion of ventilated lung units and decreasing the amount of shunt. Because a large component of gas exchange dysfunction in lung injury is attributed to intrapulmonary shunting, PEEP may relieve hypoxemia in these cases without requiring the use of high oxygen concentrations. Some clinicians will also use PEEP in other ways, such as (1) reducing the work of breathing in patients manifesting intrinsic PEEP from obstructive lung disease; and (2) decreasing intrathoracic venous return (preload) in patients with congestive heart failure.

Ventilator modalities also differ in scheduling when mandatory breaths (driven entirely by the ventilator) are given. A mandatory breath can be triggered by the patient's effort (assisted) or the ventilator breaths can be delivered at a set rate (controlled). The ventilator can be set to assist every breath (continuous mandatory ventilation) or only a set number of breaths per minute (synchronized intermittent mandatory ventilation). Using either mode, if the patient does not trigger assisted breaths at or above a rate specified, the machine delivers controlled breaths at that rate. Usually, the patient receives some combination of assisted and controlled breaths, depending on set ventilator rate and the patient's intrinsic respiratory rate. Patients receiving only assisted (self-initiated) breaths can become fatigued because, although assisting the breath decreases the work of breathing, it does not entirely rest the muscles of respiration. Once the diaphragm begins an inhalation, it continues to contract throughout the entire inspiratory cycle. One approach to resting the diaphragm is to set the ventilator rate such that most breaths are controlled (machine initiated).

Another approach to decrease the work of breathing uses a nearly opposite strategy: pressure support is used to reduce or eliminate mandatory breaths and aid the patient's spontaneous breathing. In pressure support ventilation mode, the ventilator must be triggered by patient effort. Once triggered, it provides a flow rate that varies with the difference between the airway pressure and the preset target pressure. The result is a rapidly rising upward ramp of pressure. Inspiration is terminated when the flow drops below a threshold level or a fraction of the peak inspiratory flow. When ventilated using high-level pressure support, the patient has substantial breath-by-breath control over inspiratory flow rate, tidal volume, inspiratory time, and respiratory rate. Awake patients almost universally describe this mode of ventilation as more comfortable than conventional volume-cycled mechanical ventilation, probably because the increased responsiveness of the ventilator in this mode leads to improved synchronization of the mechanical ventilator to the patient's spontaneous effort. The patient wastes less energy *fighting the ventilator* and the respiratory muscles are partially unloaded. Pressure support ventilation also allows the patient to vary the inspiratory flow rate, tidal volume, and inspiratory time from breath to breath, and, therefore, it is perceived by the patient as a much more natural pattern of breathing and more comfortable. This improved synchronization of mechanical ventilation may have the additional benefit of reducing barotrauma in patients who can be ventilated using pressure support. This mode is most effective with patients who have good respiratory muscle strength and high ventilatory drives (e.g., acquired immunodeficiency syndrome patients with pneumocystis pneumonia) and allows ventilatory support of these patients without levels of sedation that impair interaction with visitors and staff.

The limitations of high-level pressure support ventilation include the inability to use this mode in patients who are not able to maintain a sufficient respiratory rate (those who are obtunded, sedated, or given neuromuscular blocking agents) and the requirements for patient effort on each breath, which does not allow complete respiratory muscle rest and can precipitate respiratory muscle exhaustion.

Regardless of the modality chosen, matching the ventilator response to the patient's demand reduces the work performed by the respiratory muscles and may prevent respiratory muscle fatigue. The patient perceives the ventilator's response on each breath

in four ways: (1) the energy necessary to begin inspiratory flow; (2) the rate at which inspiration flow actually occurs given the level of muscle effort expended; (3) the duration of inspiratory flow (inspiratory time); and (4) the volume inspired. When the response of the ventilator fails to match the patient's demand, the work performed by the patient increases, ventilatory drive increases, and the patient becomes uncomfortable and may begin to fight the mechanical ventilator. Mechanical ventilators differ in their responsiveness to patient effort in their inspiratory triggering mechanisms, inspiratory demand values, and mechanisms of ending the inspired breath.

When a mechanical ventilator is assisting the patient's breath, it must *sense* that the patient has begun inhaling and initiate the machine-driven breath using an inspiratory triggering mechanism. For many ventilators, the breath is triggered once the patient's spontaneous efforts exceed a preset negative pressure. For earlier generations of mechanical ventilators, this threshold was –2 cm H_2O or more. Newer generations of mechanical ventilators have thresholds that can be set as low as –0.5 cm H_2O. In addition, a drop in the flow passing by the endotracheal tube can also trigger ventilators. Flow triggering may make the ventilator more sensitive to the patient's inspiratory effort and, by using software to drive the pressure at the airway opening to a slightly positive value, further reduce the patient's work during spontaneous breathing. The result is a virtual elimination of the ventilatory work added by the mechanical ventilator circuit during spontaneous breathing.

The work performed by the patient increases when the flow provided by the mechanical ventilator lags behind that demanded by the patient. Inspiratory demand valves on older models of many mechanical ventilators required greater effort to produce higher flows. More recently, ventilator inspiratory flow valves have been designed to increase flows with much less effort. Pressure support provides an even further reduction in inspiratory work by increasing the inspiratory flow in the airway to maintain a positive pressure, allowing the ventilator to provide some of the work of breathing without controlling the patient's breathing pattern.

Synchronization between the patient and the mechanical ventilator is likely to be enhanced in a new generation of mechanical ventilators currently available. Complex software algorithms and rapid feedback mechanisms to control airway pressure and flow allow these ventilators a great deal of flexibility to adjust their function to patient demands. One such strategy made possible by these developments is proportional assist ventilation, which is designed to provide a fixed proportion of the energy required for ventilation regardless of the size of the tidal volume generated or minute ventilation required. The energy required to move the respiratory system during ventilation can be divided into that part required to overcome the elastic recoil of the lung and chest wall and that part required to overcome the resistance to airflow through the airways of the lung. A proportional assist mechanical ventilator continuously adjusts the pressure it provides throughout inspiration, calculating at each adjustment both the pressure required to drive the instantaneous airflow and the pressure required to support the current inspired volume.

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59. MECHANICAL VENTILATION: WEANING AND COMPLICATIONS

Timothy A. Morris and David M. Burns

Mechanical ventilation itself poses an increased risk for serious complications and should be discontinued as soon as it is safe to do so. Unnecessarily prolonged mechanical ventilation can be minimized by (1) frequently assessing the ventilated patient to determine when *weaning* should be undertaken; and (2) weaning as rapidly as can be tolerated by the patient. In general, the reasons for mechanical ventilation dictate both the complications of mechanical ventilation and the method of weaning. Patients are placed on mechanical ventilators because of (1) failure to maintain adequate arterial oxygenation on supplemental oxygen; (2) failure to maintain adequate alveolar ventilation (excrete carbon dioxide); or (3) therapeutic objectives not directly related to gas exchange (e.g., hyperventilation for head trauma, paralysis for tetanus). Several indications can coexist; however, one indication usually predominates.

The complications associated with endotracheal intubation are common to all ventilated patients and include sinusitis, laryngeal injury, and tracheomalacia (see Chapter 57).

Patients with hypoxic ventilatory failure often require high fractional inspiratory oxygen concentrations (F_{IO_2}) and elevated peak and end-expiratory ventilatory pressures. The inhalation of an F_{IO_2} above 0.5 for extended periods increases the risk of oxygen toxicity and pulmonary fibrosis. In addition, the use of an F_{IO_2} of 1.0 (i.e., 100% oxygen) can result in an increased shunt fraction because of resorption atelectasis involving segments of the lung containing low ventilation-perfusion ($\dot{V}/\dot{Q}$) units. The problems associated with high inspiratory and expiratory pressures include hemodynamic compromise and barotrauma. High inspiratory pressure and positive end-expiratory pressure (PEEP) can unpredictably diminish cardiac output and blood pressure. Although PEEP reduces intrapulmonary shunting, it also may lead to (1) a fall in left ventricular compliance and right atrial venous return; (2) an increase or decrease in pulmonary vascular resistance; and (3) overdistention and injury of unimpaired (*normal*) alveolar units. The net effect on cardiac output and gas exchange is usually impossible to predict for an individual patient. Therefore, most patients with severe hypoxic ventilatory failure who receive high levels of PEEP will require systemic arterial and pulmonary artery catheterization for repeated measurements of hemodynamic parameters and gas tensions. During the initial management of patients requiring a very high F_{IO_2}, systemic oxygen delivery (arterial oxygen content times cardiac output) generally can be maximized by adjusting the levels of PEEP and by simultaneously expanding intravascular volume or pharmacologically enhancing cardiac output. When hemodynamic stability is achieved, efforts should be aimed at decreasing the F_{IO_2} to a safer level (below 0.7) while maintaining oxygen delivery.

The incidence of barotrauma in these patients is exceptionally high and correlates with mean and peak airway pressures. Pneumothorax can be dramatic and associated with vascular collapse, as in tension pneumothorax, or it can be a subtle roentgenographic finding caused by the limited potential for the severely damaged lung to collapse. The presence of a chest tube (either prophylactic or therapeutic) does not guarantee that another pneumothorax will *not* develop in the same hemithorax; in fact, patients with severe acute respiratory distress syndrome may require multiple chest tubes bilaterally. If a bronchopleural fistula develops, ventilation can be further compromised.

In cases of hypercapnic ventilatory failure caused by obstructive lung disease, mechanical ventilation also can reduce cardiac output caused by the sudden increase in intrathoracic pressure (with decrease in venous return). This reaction is usually limited to patients with at least mild hypovolemia at the time of intubation; it responds readily to volume repletion. Barotrauma occurs less often in these patients with hypoxic ventilatory failure and is probably related to localized differentials in alveolar pressure and distention, rather than to absolute transpulmonary pressure. The markedly distorted lung architecture in these patients can lead to barotrauma at much lower pressures.

Intubated patients of all types are at an increased risk of infection. Bacterial overgrowth of gastric contents following adjustment of gastric pH with antacid or H_2 blocking agents, which is a major source of nosocomial pneumonias, can be minimized by substituting sucralfate for these agents as prophylaxis for gastric bleeding. Malnutrition can be a major problem in patients requiring prolonged ventilatory support. Nutritional support should begin as soon as possible in any patient in whom prolonged ventilatory support is contemplated.

In the final group of patients in whom special indications prompt ventilatory support, the complications are often directly related to the therapeutic modalities used rather than to the ventilator *per se*, as these patients often enter the intensive care unit (ICU) with relatively normal lungs. The consequences of ventilators disconnected from the paralyzed patient are tragic; appropriate safeguards, including carefully tested apneic alarms, should be initiated in this situation. The application of barbiturate coma for head trauma patients, particularly in conjunction with rigorous maintenance of the head-up posture, can lead to a greater than normal problem of maintaining bronchial hygiene, even in those patients with normal lungs. This group can develop lobar collapse and gram-negative pneumonia if careful prophylactic measures are not initiated.

In addition to the complications already mentioned, patients on mechanical ventilation can also experience cardiac arrhythmias, seizures, and gastrointestinal bleeding. Arrhythmias can be related to hypoxemia, hypokalemia, and other electrolyte disturbances and the use of drugs (e.g., β-agonists, aminophylline) with an arrhythmogenic potential. Seizures can occur because of prior hypoxemia, too rapid reversion of chronic hypercapnia, or theophylline excess. Gastrointestinal bleeding from gastritis or frank gastric ulceration is common; however, the mechanisms responsible are not clear. Antacids and H_2-receptor blockers appear to reduce the incidence of bleeding, particularly in patients with acute central nervous system disease (e.g., head trauma, cerebrovascular accidents).

Mechanical ventilation should be discontinued as soon as it is safe to do so. Although this usually requires, to some degree, the reversal of the primary causes for mechanical ventilation, the causes need not be entirely resolved before patients can be safely extubated. Furthermore, although the term *weaning* is commonly used to describe the process of ventilator discontinuation, gradual tapering of ventilator support may not be necessary in many patients. Depending on the patient, weaning can have two possible purposes: (1) assure the medical team that mechanical ventilation is no longer necessary; and (2) gradually train the respiratory muscles to assume the entire work of breathing.

Weaning can account for as much as 40% of the time on mechanical ventilation, and methods to decrease time spent weaning may reduce complication rates and save considerable expense. Timing is a major issue. The patient who is extubated too early, requiring reintubation, is subject to difficulties in obtaining an airway, laryngeal injury, aspiration pneumonia, and cardiac ischemia, all of which lead to a greater risk of mortality. Conversely, the patient who is left on mechanical ventilation too long risks nosocomial pneumonia, tracheal injury, and the other complications mentioned above.

Successful extubation requires that the work needed for breathing is substantially less than the capacity to breath. The work of breathing depends on factors such as (1) the amount of gas exchange required, which in turn depends on O_2 consumption and CO_2 production; (2) gas exchange efficiency, including the (A-a) O_2 gradient and ventilation dead space to tidal volume ratio (V_D/V_T); and (3) the physical work required to inflate the lungs, such as lung and chest wall compliance. The capacity to breathe, in turn, depends on (1) central nervous system mechanisms to control breathing; (2) respiratory muscle strength; and (3) endurance. Despite a great deal of clinical

investigation, it is still difficult to predict when the balance of these factors will permit discontinuation of mechanical ventilation in particular patients.

The good news for clinicians is that complex, time-consuming, and often-inconsistent methods of weaning are largely being replaced by simpler algorithms that are at least as effective. Essential to the process is the categorization of patients into one of four basic groups: (1) those in whom immediate extubation is likely to be successful; (2) those in whom weaning is progressing toward the goal of extubation; (3) those who are not progressing, in whom further investigation is necessary; and (4) those in whom weaning of any type is contraindicated.

The first step is to identify patients in the last group, in whom weaning would be likely to cause harm. This group generally has one or more of the following problems: (1) inadequate gas exchange, evidenced by a low Pa_{O_2}/F_{IO_2} ratio or the requirement for high levels of PEEP; (2) inability to cough or clear secretions during spontaneous breathing; (3) instability such as shock or hypotension; (4) severe muscle weakness or paralysis; (5) sedation or obtundation; (6) major procedures planned in the near future; (7) unstable myocardial ischemia; or (8) elevated intracranial pressure. Patients with these contraindications to weaning should be monitored daily for signs of resolution. Those without them should begin weaning. This aggressive approach to initiating weaning is safe and shortens the duration of mechanical ventilation.

The next step is to distinguish those patients who are ready for immediate discontinuation of mechanical ventilation from those in whom intermediate steps are necessary. The patient's respiratory performance (while receiving minimal support from the ventilator) may predict when extubation will be tolerated. A variety of *weaning parameters* have become popular (e.g., minute ventilation, respiratory rate, and inspiratory pressures). A simple and accurate predictor is the *rapid shallow breathing index*, representing the ratio of the respiratory rate to the tidal volume (f/V_T). Our preference is to test the f/V_T during brief periods of spontaneous breathing (on T-piece or with a low amount of pressure support) at least once daily. Patients with low f/V_T ratios are allowed to continue spontaneous breathing and, if they tolerate the *sprint* for 1 to 2 hours, are extubated. Those in whom the initial f/V_T is high require further steps to be liberated from mechanical ventilation.

For those patients who cannot be extubated immediately, intermediate steps may be necessary. Whether the patient's performance during these weaning steps is the cause of or the result of improved respiratory status is controversial. Options include (1) periodically *sprinting* the patient with intervals where the ventilator provides lower levels of assistance, using intermittent mandatory ventilation (IMV), pressure support, or T-piece with humidified oxygen flowing past; or (2) intermittently decreasing the assistance from the ventilator, allowing the patient to gradually assume the burden of ventilation, using IMV, pressure support, or a combination of the two. Although no general consensus exists on the relative merits of these two strategies, recent evidence appears to favor periodic sprinting. Whatever the modality chosen, a few points should be considered when designing a weaning program. First, patients may improve faster than expected, and any weaning process should include routine screening to identify those who have developed the ability to breathe without mechanical assistance. Conversely, the patient should not be allowed to work the respiratory muscles to exhaustion, as a prolonged period of rest may then be necessary before the next attempt at weaning. Finally, the clinician must routinely evaluate each patient's progress during weaning, and identify those who are not advancing toward extubation. Patients who fail to progress during weaning should be reassessed to disclose any reversible causes of prolonged dependency on the ventilator.

Weaning is best begun early in the morning when the patient is rested and the ICU staff maximally staffed. The patient should be placed on an F_{IO_2} that is 0.1 higher than the maintenance level and observed both clinically and with oximetry. Clinical evidence of respiratory muscle fatigue includes tachycardia, an increase in the respiratory rate to 35 or above, or complaints of severe dyspnea. In most patients, these signs indicate the need to return to the prior level of ventilatory support regardless of blood gases. However, a Pa_{O_2} of less than 60 mm Hg or a pH less than 7.25 is also a clear indication to stop the weaning interval.

Psychological factors can be a major problem for some patients during weaning. An attempt should be made to carefully explain to the patient the weaning process and

the likely sensations. The development of trust between the patient and staff is particularly important. Continued reassurance and confidence will often achieve the best results.

Failure to advance toward liberation from the ventilator can generally be traced to insufficiencies of gas exchange, ventilatory drive, muscle strength, or endurance. In general, a Pa_{O_2} greater than 60 mm Hg on 35% oxygen or less should be enough to permit spontaneous breathing. True neurologic abnormalities of ventilatory drive are rare; when present, they are usually inconsistent with successful weaning. Secondary abnormalities of respiratory drive are common, however, and are usually reversible. The most common secondary abnormalities are metabolic alkalosis and oversedation. One hallmark of a suppressed respiratory drive is the presence of an elevated $Paco_2$ during weaning without a corresponding increase in respiratory rate. Muscle strength and mechanical advantage also are critical to successful weaning and should be considered in relation to the work the muscles will be obligated to perform. The maximal inspiratory pressure is a simple measure of muscle strength, and the peak pressure needed by the ventilator to move a tidal volume breath provides a gross approximation of the work the muscles will have to perform. Useful rules of thumb are that the maximal inspiratory pressure should equal the ventilatory peak pressure and that the vital capacity should at least equal the tidal volume provided by the ventilator.

Careful examination of the patient during weaning may help explain the reasons for failure to progress. The pattern of muscle fatigue during weaning is usually characterized by a decreasing tidal volume and an increasing respiratory rate. An important warning sign is the development of a paradoxical motion of chest and abdomen, in which the abdomen moves inward during inspiration, suggesting diaphragmatic fatigue. These changes may precede $Paco_2$ elevation and indicate the need to return the patient to a higher level of ventilatory support. A number of factors can contribute to muscle weakness and fatigue: inadequate nutrition, respiratory muscle deconditioning and atrophy, electrolyte depletion (potassium, phosphate, magnesium, and calcium), hormonal imbalance (thyroid or steroid), neural and neuromuscular lesions (including spinal cord lesions), and increased lung volume. Many of these problems are easily detected once they are considered. Correcting them can make a profound difference in a patient's ability to wean.

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60. NUTRITIONAL SUPPORT OF THE CRITICALLY ILL PATIENT

David P. Kupferberg, Dana Richards, and William R. Auger

Nutritional depletion, which is often present in the critically ill patient, can be associated with increased nosocomial infection, reduced or delayed wound healing and tissue repair, loss of muscle strength, and diminished activity. These added comorbidities can significantly delay recovery from the inciting illness, complicate weaning from mechanical ventilation, and prolong rehabilitation. Delivery of aggressive nutritional support may improve outcome and diminish mortality in these patients.

Protein energy malnutrition (PEM) describes a broad spectrum of clinical conditions. Severe PEM is chronic in nature, clinically apparent, and characterized by somatic protein and fat store depletion. The cachexia or severe wasting is known as *adult marasmus*. Early identification of such patients assists in tailoring corrective nutritional therapy to prevent complications from aggressive delivery of nutritional support manifesting in the refeeding syndrome. The refeeding syndrome is evidenced by hypokalemia, hypophosphatemia, and hypomagnesemia and is caused by insulin transport of glucose into the cell membrane. Feeding malnourished patients should be initiated slowly and monitored closely. Adult kwashiorkor is another form of PEM that is less apparent clinically but associated with increased morbidity and mortality. This develops acutely and is characterized by hypoalbuminemia, depressed cellular immunity, and expansion of extracellular water. The type of nutritional deficit found in patients with catabolic disease depends on the underlying disease state. Patients with chronic disease are more likely to present with marasmic-type malnutrition and subsequently develop kwashiorkorlike malnutrition as the result of acute illness. In contrast, trauma patients who are adequately nourished before injury may develop kwashiorkorlike malnutrition.

The metabolic response to critical illness is generally characterized by hypermetabolism, elevated body temperature, accelerated protein breakdown and nitrogen loss, and disturbances of carbohydrate, amino acid, and fat metabolism. The degree of hypermetabolism is proportional to the severity of illness, with energy expenditure ranging from 5% to 100% over basal requirements. However, the hypermetabolic response does appear to reach a maximal plateau of approximately twice the basal metabolic rate even in the most intense hypermetabolic conditions. This calorie demand during critical illness is accompanied by an increase in glucose production via glycogenolysis and gluconeogenesis. This increased glucose production is not readily suppressed by exogenous glucose or insulin production.

Increased protein demands that accompany critical illness also reflect the underlying disease and specific factors associated with it. Increased nitrogen catabolism has been documented in conditions such as sepsis, burn injury, trauma, and head injury. Increased nitrogen excretion closely follows an augmented metabolic rate, yet can be proportionally greater than the increase in energy expenditure. This catabolic state results in a redistribution of lean body mass and reduction in circulating hepatic transport proteins. Skeletal muscle protein stores are rapidly mobilized and transported to the liver as substrates for fuel and to areas of active visceral and wound protein synthesis. If prolonged, this endogenous protein catabolism, or *autocannibalism*, can result in major organ dysfunction. Recent attention has been focused on interleukin-1 (IL-1) and tumor necrosis factor as mediators of endogenous protein catabolism, where their proteolytic effects are seemingly synergistic. Protein utilization is also altered as a result of impaired insulin-mediated amino acid uptake and insulin-mediated protein synthesis.

In addition to increased demands for both protein and calories, altered lipid utilization occurs in patients with critical illness. For example, in sepsis, lipolysis is increased because of activation of sympathetic nerves in adipose tissue and increased production of catabolic hormones such as epinephrine, glucagon, and cortisol. However, free fatty acids and triglyceride utilization can be impaired because of a reduction of lipoprotein lipase activity.

Despite physician awareness that profound metabolic derangements can occur in critical illness, compromised delivery of nutrition can result from common oversights. First, the magnitude of nutritional demand is often unrecognized. Second, early nutritional support may not occur because of an assumption that the illness will be self-limited.

The most important goals of nutritional support in patients with critical illness are to (1) promptly provide adequate calories and protein; (2) minimize the effects of hypercatabolism; and (3) prevent micronutrient deficiencies.

The provision of adequate calories is an essential component of nutritional support. Adequate caloric delivery reduces endogenous tissue breakdown and prevents gluconeogenesis, whereas the delivery of excessive total calories has been associated with increased carbon dioxide production and hepatic steatosis. It is important, therefore, to provide sufficient amounts of calories without overfeeding. In the clinical setting, energy requirements can be determined using one of two general methods: (1) indirect calorimetry or (2) predictive equations. The measurement of energy expenditure by indirect calorimetry is optimal in determining the energy requirements of patients with catabolic illness. Indirect calorimetry uses bedside analysis of the oxygen and carbon dioxide content of respiratory gas samples. This permits calculation of resting energy expenditure and the respiratory quotient (ratio of carbon dioxide produced to oxygen consumed), which can be used to guide appropriate nutritional support. The accuracy of indirect calorimetry measurements in critically ill, mechanically ventilated patients requires attention to multiple factors such as leaking chest or endotracheal tubes, bronchopleural fistulas, and mechanical ventilation with high fractional inspired oxygen concentrations (FIO_2) or positive end-expiratory pressures.

Historically, basal energy expenditure has been calculated using the Harris-Benedict equation and adjusted using activity and stress factors. Although predictions for energy expenditure are within 10% in more than 90% of nonstressed individuals with normal body composition, significant individual and day-to-day variability in measured energy expenditure has been reported in critically ill patients. New equations have been developed utilizing indirect calorimetry as the *gold standard*. The Ireton-Jones equations were developed using data from 200 critically ill and burned patients classified as obese (>130% ideal weight) or nonobese; the equations were subsequently tested on 100 patients. They can be used for ventilator-dependent or spontaneously breathing patients. When using predictive equations, attention to medications, ventilator settings, and course of treatments should be considered. For example, paralytic drugs decrease resting energy expenditure and continuous positive airway pressure support increases energy needs caused by the increased work of breathing.

Ireton-Jones equations
Spontaneously breathing: EEE = 629 − 11A + 25W − 609O
Ventilator dependent: EEE = 1784 − 11A + 5W + 244G + 239T + 804B

Where

EEE = estimated energy expenditure (kcal/d)
A = age (years)
W = weight (kg)
O = presence of obesity >130% IBW (0 = absent, 1 = present)
G = gender (0 = female, 1 = male)
T = diagnosis of trauma (0 = absent, 1 = present)
B = diagnosis of burn (0 = absent, 1 = present)

Harris-Benedict equations
Males: EEE = 66.47 + (13.75 × weight [kg]) + (5.0 × height [cm]) − (6.76 × Age [y])
Females: EEE = 665.10 + (9.56 × weight [kg]) + 1.85 × height [cm]) − (4.68 × age [y])

Adequate nonprotein calories should be provided by a combination of carbohydrate and fat. Glucose exerts a greater protein-sparing effect than fat when provided in quantities up to approximately 60% of total calorie requirements. Newer recommendations for glucose delivery are as low as 4 mg/kg/min to prevent the deleterious effects of hyperglycemia. The remainder of total calorie needs should be provided as protein

and fat. Considering the type and amount of fat delivery in catabolic disease may be important. For example, high doses of omega-6 fatty acids can cause hypoxemia, bacteremia, and suppression of in vitro tests of immune function. The use of sedatives such as propofol, based in 10% lipid emulsion, should be accounted when prescribing nutrition support (1.1 kcal/ml).

The optimal amount and type of protein needed by critically ill patients remains controversial. Although adaptive mechanisms significantly reduce endogenous protein catabolism in chronic starvation, significant metabolic and physical protein losses occur unabated in these patients. Cumulative nitrogen losses ranging from 136 to 200 g/10 days have been reported in patients with peritonitis, multiple trauma, major burn, and severe head injury. In patients with critical illness, the delivery of exogenous protein and glucose minimizes but does not eliminate catabolism of endogenous protein stores. Nutritional support can reduce net protein losses by half in patients with serious sepsis. This reduction in net protein losses is caused by an increase in whole body protein synthesis rather than simply by a decrease in whole body protein catabolism. In burn patients, protein synthesis increased to a level equal to the protein catabolic rate when protein delivery was 1.5 g/kg of body weight, whereas a net gain of protein was observed with protein delivery of 2.2 g/kg of body weight. Similarly, in trauma patients, protein delivery of 1.7 g/kg of body weight resulted in a significant reduction in net protein losses from increased protein synthesis. Therefore, recommendations for protein delivery in most critically ill patients range from 1.5 to 2.0 g/kg/d of body weight, which represents a nonprotein calorie:nitrogen ratio of 140:1 to 100:1. Investigators studying hypermetabolic states have recommended protein delivery of more than 2.0 g/kg of body weight in an attempt to induce an anabolic state. Protein delivery should be individualized and periodically adjusted based on the results of nitrogen balance studies and visceral protein status markers.

The route of nutritional support (enteral versus parenteral) is also an important consideration in critically ill patients. Parenteral nutrition has been associated with gut mucosal atrophy, reduced levels of secretory IgA, increased bacterial and endotoxin translocation, and an exaggerated hormonal and metabolic response to septic challenge. Therefore, enteral nutritional support should be used unless contraindicated by the following conditions: complete intestinal obstruction; ileus (unless localized to stomach); high-output intestinal fistulas (>500 ml/d); severe intractable diarrhea (>1500 ml/d); severe acute pancreatitis; initial phase of short-bowel syndrome; or severe hemodynamic instability. In addition to decreased costs, enteral nutrition is beneficial because it preserves gastrointestinal barriers and host defense mechanisms. Furthermore, the provision of early nutrition support may blunt the catabolic processes previously discussed. Gastric or intestinal access for enteral nutrition is acceptable. Gastric residuals may preclude adequate provision of nutrients, but can be overcome by using promotility agents such as metoclopramide. However, nutrient goals can be more rapidly attained by using transpyloric feeding tubes, which can be successfully inserted at bedside. Polymeric formulas can be used transpylorically without complications.

Nutritional assessment techniques useful in hospitalized patients include measurements of anthropometrics, visceral proteins, and nitrogen balance. Anthropometric measurements include current body weight and height, triceps skinfolds, midarm circumference, and midarm muscle circumference. An initial assessment of ideal body weight, usual weight, and dry body weight is useful in determining initial nutritional status. However, the presence of fluid overload and fluid shifts will affect these measurements and results should be interpreted with caution. Arm circumference and skin-fold measurements may not be particularly useful because (1) they do not respond acutely to critical illness and (2) the standards have been based on healthy adults.

Hepatic transport proteins such as serum albumin, transferrin, and prealbumin have been used to monitor visceral protein status in critically ill patients. Serum albumin is a valuable prognostic indicator in predicting increased morbidity and mortality. A long half-life of approximately 20 days and non-nutritional factors (e.g., hydration status, presence of infection, stress, and the use of blood products) limit its clinical validity as a marker of short-term visceral protein repletion. Transferrin is used infrequently; it has a half-life of 8 to 10 days and smaller body pool than serum albumin, but non-nutritional factors and iron status affect serum levels. The half-life (2–3 days)

and small body pool of serum prealbumin allow its use as a short-term nutritional marker of visceral protein status. Levels of serum prealbumin increase more rapidly in response to nutritional support compared with transferrin, yet prealbumin levels are also affected by non-nutritional factors such as inflammation, liver disease, and renal dysfunction. It is probably the most reflective visceral protein marker when evaluating the adequacy of nitrogen provision. As a result, caution should be used in interpreting serum albumin, transferrin, and prealbumin levels in patients with critical illness.

Determining nitrogen balance is a useful tool to assess the degree of catabolism and guide the delivery of nutritional support in critically ill patients. In patients with normal renal function, nitrogen balance can be calculated by subtracting nitrogen losses from nitrogen delivered. Losses are estimated from 24-hour urinary urea nitrogen, adding a factor to approximate gastrointestinal, skin, and nonurea urinary nitrogen losses (creatinine, ammonia, uric acid, amino acids). Gastrointestinal and skin losses of nitrogen are generally estimated to be 2 g/d, yet may be increased as a result of diarrhea, fistula drainage, major burns, or nasogastric suction. Insensible nitrogen losses are usually estimated at 4 g/d to account for this variability. The validity of using urinary urea nitrogen values to calculate urea nitrogen losses is compromised when creatinine clearance falls below 50 ml/min. Protein balance calculations, therefore, are modified in patients with acute renal failure because of decreased urinary urea clearance. The clinical goal is nitrogen equilibrium or a positive nitrogen balance. As 24-hour urinary urea nitrogen accuracy can vary because of the collection process, a visceral protein marker can be helpful for monitoring purposes.

$$\text{Nitrogen balance} = N_{2\,in}\,(\text{g protein}/6.25) - N_{2\,out}\,(24 \circ \text{UN g/TV} + 4)$$

Future directions in nutritional support include the use of various agents to minimize endogenous catabolism; enhance anabolism, pharmacologic, and nutritional immunomodulation; and improve nutritional assessment techniques. Growth hormone has been reported to decrease cumulative nitrogen excretion. However, a recent multicenter trial revealed an increased mortality rate when growth factor was used in critically ill patients. Monoclonal antibodies against tumor necrosis factor and endotoxin can interrupt the cytokine events associated with septic shock, thereby lessening hypermetabolism and proteolysis. Similarly, various prostaglandins and α-adrenergic agents can be used to reduce the catabolic state.

Nutritional immunomodulation can be accomplished by providing specific nutrients that may be conditionally essential in patients with critical illness. Glutamine is thought to be a conditionally essential amino acid in stress and an important transporter of nitrogen from the periphery to visceral organs. Glutamine is also the preferred fuel for enterocyte proliferation. Total parenteral nutrition (TPN) with supplemental glutamine has been associated with improved nitrogen balance, reduced infectious complications, and reduced hospital stay, when compared with standard TPN in a randomized, controlled trial of patients undergoing bone marrow transplantation. However, because evidence supporting immunomodulated formulas is not yet compelling, their use should be considered controversial.

Improved nutritional assessment tools can enhance the ability of clinicians to provide adequate nutritional support. For example, bioelectric impedance analysis can noninvasively detect alterations in fluid distribution following critical illness and monitor the effects of nutritional therapy on body cell mass.

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61. PULMONARY OXYGEN TOXICITY

David P. Kupferberg and William R. Auger

Application of high concentrations of oxygen supplementation, which is often necessary to reverse acute hypoxemia, can lead to numerous physiologic and cellular alterations and lung injury. The actual incidence of these events is unclear because the primary pulmonary process prompting oxygen therapy can obscure or alter the manifestations of oxygen toxicity. However, evidence suggests that a *subclinical* alteration in cellular function may result from exposure to oxygen concentrations exceeding 50%, potentially affecting the reparative process following the inciting acute lung disease. It is possible that some degree of oxygen-induced pulmonary injury is operative in every patient exposed to high concentrations of inspired oxygen.

The pathogenesis of oxygen-associated lung injury appears to be caused by the excessive generation of *free oxygen radicals* occurring in the setting of hyperoxia. The production of these partially reduced oxygen moieties (superoxide anion, hydrogen peroxide, and hydroxyl radical) overwhelms cellular enzymatic defenses (superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic scavengers (e.g., α-tocopherol acetate). The damaging effects of these radicals include membrane lipid peroxidation, protein sulfhydryl oxidation leading to critical enzyme inactivation, and alteration of nucleic acids. These events interrupt normal cellular function and, if sufficiently severe, lead to cellular death. In addition to these direct cytotoxic effects, hyperoxia can cause tissue damage through indirect mechanisms. Alveolar macrophage function is altered following hyperoxic exposure. Chemotoxins and other humoral factors are released and stimulate neutrophil adhesiveness and superoxide generation, contributing to capillary endothelial and alveolar epithelial cell injury. The stimulated macrophages also may release increased amounts of fibronectin and promote growth of fibroblasts early in the course of oxygen exposure. In animal models of hyperoxia, increased expression of tumor necrosis factor (TNF) and the cytokines, interleukin-1 and interleukin-6, has been described. It appears that TNF not only exhibits a direct cellular toxic affect via oxidative mechanisms, but early on induces manganous superoxide dismutase (Mn SOD) that is responsible for scavenging superoxide radicals. Furthermore, neutrophil sequestration into lung regions exposed to high concentrations of oxygen is at least partially modulated by the expression of intercellular adhesion molecules (ICAM-1) on both endothelial cells and type II pneumocytes. The

participation of type II pneumocytes in the inflammatory response of hyperoxia can be of critical importance in alveolar repair following sublethal injury.

Four clinical syndromes resulting from exposure to normobaric hyperoxia have been described: (1) acute tracheobronchitis; (2) absorption atelectasis; (3) an acute alveolar lung injury (acute respiratory distress syndrome [ARDS]); and (4) bronchopulmonary dysplasia. Although the last is primarily the end result of the neonatal respiratory distress syndrome, similar chronic fibrotic changes have been described in the adult exposed to high partial pressures of inspired oxygen. These findings, however, may simply represent the nonspecific result of the reparative phase following an acute alveolar-interstitial injury.

The acute clinical syndromes are better understood after examining the physiologic and pathologic consequences of hyperoxic exposure. In normal subjects breathing 100% oxygen, the earliest manifestation of adverse effects is tracheobronchial irritation. Bronchoscopic evidence of tracheitis has been observed as soon as 6 hours following exposure to 90% to 95% oxygen. This has been accompanied by a reduction in tracheal mucociliary transport, although pulmonary function tests remain normal. After more lengthy exposure (6–24 hours), a reduction in vital capacity is seen, believed to be related primarily to absorption atelectasis. Furthermore, within 6–12 hours, studies in normal men breathing 100% oxygen and forced to breathe deeply periodically have shown no alteration in lung function when measuring alveolar-arterial oxygen tension difference ($P[A\text{-}a]O_2$), physiologic shunt, pulmonary vascular resistance, or extravascular lung volume. However, extending the duration of oxygen exposure beyond 24 hours has been associated with a decrement in lung compliance, widening of the $P(A\text{-}a)O_2$ gradient, and a decline in carbon monoxide diffusing capacity.

In the clinical arena, pulmonary physiologic measurements of intubated patients exposed to hyperoxia have varied in their results, likely because of the underlying clinical problems. Some evidence suggests that beyond 48 hours of hyperoxia (inspired oxygen concentration [F_{IO_2}] = 1.0), a decline in Pa_{O_2}, an increase in intrapulmonary shunt, and radiographic evidence of interstitial infiltrates can be observed.

The pathologic changes following normobaric hyperoxic exposures have been well described in numerous animal species. The changes seen in humans are similar; they are affected by the dose of oxygen, the length of exposure, and, speculatively, the presence of the inciting acute lung injury. During the *early*, or *initiation, phase* of oxygen-induced lung injury, oxygen radical generation and altered cellular metabolism occur with no discernible morphologic changes. In the sequence of injury, the pulmonary capillary endothelial cell appears to be the site of the initial hyperoxic damage. Early on, as demonstrated by studies with cultured human pulmonary artery endothelial cells, a reversible impairment of cell growth can result following 48 hours of exposure to oxygen concentrations as low as 60%. However, with continued exposure to high oxygen concentrations, an *exudative*, or *inflammatory, phase* can intervene. This is characterized by the development of interstitial edema and inflammatory cell infiltration, hyaline membrane formation along alveolar surfaces, endothelial cell destruction and fibrin thrombi deposition, and focal hemorrhage. It is also during this destructive stage that a significant injury occurs to alveolar type I epithelial cells. These changes have been described in intubated humans exposed to 60% to 100% oxygen for as short a time period as 3 days. If hyperoxic exposure continues, the exudative and destructive stage is followed by a *proliferative phase* characterized by hyperplasia of type II pneumocytes and of alveolar septal cells. Depending on the extent and duration of injury, a fibrotic reaction involving the lung interstitium can ensue. If the lung injury and repair process are extensive, parenchymal destruction and air space enlargement—an emphysematouslike process—can be seen. The pathologic sequence resulting from oxygen-induced injury parallels that following a number of insults, such as radiation exposure, ARDS, and drug-induced pulmonary disease.

Modification of oxygen's toxic effects has been reported in association with certain medications. Bleomycin, a glycopeptide antibiotic used in chemotherapy, forms a ferrous-DNA complex that generates superoxide anion. In the presence of hyperoxia, the potential adverse effects on the lung become more pronounced. Nitrofurantoin and paraquat—both metabolized through free radical intermediates—have similar synergistic toxic effects on the lung when combined with high levels of supplemental oxygen.

Despite the body of evidence describing the damaging effects of hyperoxia, clinical experience and numerous animal studies suggest that a degree of oxygen tolerance can develop in the setting of acute lung injury. A recent retrospective study found that, in patients with acute respiratory failure, the duration of exposure to an F_{IO_2} of 0.9 or greater was no different in survivors versus nonsurvivors; in fact, the total duration of exposure to an F_{IO_2} greater than 0.5 was longer in surviving patients. It is speculated that acute lung injury may protect against oxygen toxicity by the induction of certain adenosine triphosphatases (ATPases), the release of endotoxin or cytokines such as interleukin-6, and through other unknown mechanisms. Animal studies have shown that sublethal hyperoxic exposure can induce protective enzymes (e.g., catalase or glutathione peroxidase) that may enhance tolerance to subsequent exposure to lethal oxygen levels. Such tolerance in rats can be achieved by continuous exposure to 85% oxygen for several days before potentially lethal oxygen exposures. Such observations in animals have not been readily translated into practical guidelines for human prophylaxis.

Several reports in animals have documented protection afforded by sublethal endotoxin injection, even when administered by a single injection up to 24 to 36 hours following the onset of hyperoxic exposure. The mechanism appears to involve induction of intrinsic antioxidant enzymes. Numerous animal studies have shown no beneficial or protective effect from inhibitors of prostaglandin synthesis or from corticosteroids. In fact, corticosteroids have been detrimental in most trials, apparently because of an associated decrement in antioxidant enzyme activities. In one study, administering high-dose magnesium sulfate to rats exposed to 100% oxygen for 96 hours had a protective effect. Although the mechanism of efficacy was unknown, interference with the production of arachidonic acid metabolites pivotal to oxygen-induced lung injury was postulated. Finally, dietary manipulation, such as increased intake of exogenous polyunsaturated fatty acids or sulfur-containing amino acids, has shown some promise in providing a pool of oxidant targets, which may deflect oxidant injury from critical cellular constituents.

Research observations in animals have not been readily translated into clinical practice. Therapeutic trials have focused on attempts either to enhance natural antioxidant defense mechanisms or to supplement endogenous pools of free radical scavengers. Vitamin E is a free radical scavenger believed to be essential in minimizing peroxidation of unsaturated fatty acids in cellular membranes. Animal and human studies, however, suggest that, whereas vitamin E may be protective in deficiency states (e.g., preterm neonates), supplemental vitamin E in the absence of deficiency does not afford protection. An antioxidant function has been postulated for vitamin C, but no evidence indicates that its administration prevents oxygen toxicity. Intravenous administration of the antioxidant acetylcysteine has shown a protective effect against some of the physiologic consequences of hyperoxia. Recent data suggest that *overexpression* of extracellular SOD by transgenic mice mitigated lung injury after exposure to hyperoxia. However, previous attempts to deliver aerosolized SOD, both to enhance degradation of superoxide anion and to block free radical chain reactors, have failed to prevent oxygen toxicity in animals.

With questions remaining about the incidence, modulating factors, and natural history of normobaric hyperoxia in the critically ill patient, definite guidelines about *safe* levels of supplemental oxygen are difficult to define. However, certain practical guidelines can be suggested: (1) short-term exposure (24–36 hours) to an F_{IO_2} of 0.6 or above can be tolerated and is probably without long-term sequelae; (2) in the hypoxemic patient, optimization of oxygen-carrying capacity through careful attention to hemoglobin levels and cardiac output should accompany concerns about the level of supplemental oxygen; (3) measures such as positive end-expiratory pressure should be used in the setting of diffuse parenchymal lung disease in an effort to reduce F_{IO_2}; and (4) F_{IO_2} should be reduced below 0.6 as quickly as possible once adequate tissue oxygenation has been ensured.

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62. PROTOCOL-DRIVEN CARE IN RESPIRATORY THERAPY

Timothy A. Morris and Richard M. Ford

The success of complex treatment plans for pulmonary patients depends on a clear understanding between the physician making the plans and the respiratory therapist charged with implementing them. Any experienced clinician can attest to the comfort felt when working with familiar colleagues who *know the drill* concerning the treatment strategies for their patients. After years of working together, the physician learns to depend on a trusted therapist to inform him or her in advance when a therapy does not seem to be having its intended effect. Likewise, the therapist comes to know precisely how the physician views the goals of therapy and can recognize well in advance when modifications to the plan are required to ensure that the goals are met. Cooperatively developed protocols formalize and enhance this understanding of care plans between physicians and respiratory therapists.

Protocols ensure that (1) the physician's intentions are realized; (2) care is appropriate, timely, and driven by the patient's condition; (3) lower-cost alternatives are used when appropriate; and (4) most importantly, clinical conditions requiring physician notification are clear. Protocols are simply algorithmic paths that specify what care will be delivered, when it will be discontinued or altered, and when the physician will be contacted for changes in management. They cover only those alterations in care that the hospital physicians agree should always occur when the protocol criteria are fulfilled.

Once the physician establishes the need for treatment, protocols provide a means to ensure that what is supposed to happen to the patient does happen. Access to the program can be structured so the physician can request a specific therapy, specific protocol, or simply *respiratory care protocol*. If the therapist identifies the opportunity to

use a protocol of care that differs from the initial physician request, he or she contacts the physician to review and approve new or additional care plans. The protocols supplement, but never override, physician instructions; orders that deviate from the protocols continue to define the care delivered.

Physicians who use a protocol must be completely familiar with its algorithms and receive a summarized version in a concise manual (examples are included in the references). Such protocols should contain clear decision points defining when the therapist should apprise the physician of changes in patient status. The therapist should contact the physician directly if any acute deteriorations in a patient's condition occur or document the achievement of therapeutic goals and outcomes on an evaluation form. Advantages to physicians include (1) the ability to write flexible orders that can adapt to predictable changes in the patient's condition; (2) assurance that the care provided is state-of-the-art; (3) notification when the patient's status changes significantly; (4) freedom from documentation; and (5) the ability to exempt patients who do not fit the protocols.

Respiratory care protocols are developed *together* by physicians, respiratory therapists, and other members of the medical team. Their creation depends on a thorough review of published literature as well as on the savvy of experienced clinicians. Tailored to the specifics of each hospital, the protocols reflect the consensus of the medical team regarding the optimal care plans to be used *in most cases* for specific respiratory conditions. Far from superseding the involvement of the physician, it allows the physician to have active input into evaluation and treatment algorithms, as well as to specify when a protocol should be stopped and when to be notified. The clarity and detail with which these plans are made far exceed what is possible through written orders for an individual patient.

Similarly, the respiratory therapist becomes much less a provider of *ancillary service* and more an agent of the physician, ensuring that patients receive timely and appropriate interventions as outlined in the protocol. The respiratory therapist is trained to evaluate and quantitate the physiologic effects of each patient's treatment. Round-the-clock documentation of physiologic parameters can be invaluable to the care of patients with respiratory conditions. Furthermore, the therapist is able to follow a clear consensus plan on how to adjust therapy based on the *real-time* condition of the patient and previous response to treatment. Finally, the therapist has clear guidelines for when to contact the physician, when to discontinue a protocol, and when to suggest another, more appropriate protocol.

The financial pressures resulting from fixed payment reimbursement and quality care issues make it increasingly important to ensure that respiratory care services are provided only when indicated. Clinical studies have demonstrated a decrease in the utilization of respiratory care services using protocol programs to defer therapy, promote the timely discontinuance of therapy, or make a transition to therapy that does not require the same labor intensity. These reports showed no reduction in the quality of patient care, but vast reductions in overall cost of care with protocolized programs. Medical centers have reduced annual multimillion dollar respiratory care costs by up to 25% using a protocolized program that, for example, adjusts the dose and scheduling of bronchodilator administration using therapist-measured physiologic feedback parameters.

The creation of respiratory care protocols more than 20 years ago had little to do with cost reduction. The need arose as technology to support mechanical ventilation was developed and devices were designed to treat and support patients with respiratory impairments. As treatment became more complex and dynamic, caring for the respiratory patient was like hitting a moving target. Patient condition changed continuously, requiring ongoing modifications to treatment. The observation and feedback from the bedside therapist became an important asset to the physician, who could not always be in the room.

Initiating and maintaining a respiratory care protocol program requires a team effort among (1) the medical director of respiratory care; (2) a program leader to oversee planning and keep the program on track); (3) interested physicians to plan and utilize the protocols; and (4) the therapists who will execute them. Step-by-step instructions on how to plan and initiate respiratory care protocol programs, as well as detailed exam-

ples of specific protocols, are referenced below. The number of protocols implemented and the timeline for program expansion will likely depend on the readiness of the respiratory care department and physician staff. It is essential to provide specific training and competency assessment before implementing any protocol. Program development extends well beyond drafting a set of protocols. It includes defining related policies, identifying who does what, determining competencies and required training, and establishing mechanisms to monitor activities.

Protocols must be considered statements of what everyone agrees should happen when certain conditions occur. All of the *stakeholders* must be offered the opportunity to modify the protocols before their acceptance. Although attempts to gain some consensus among physicians in the institution regarding the complex aspects of respiratory care delivery may take considerable time (4–12 months), the early *buy-in* is critical. All suggestions should be incorporated or addressed in some way. All applicable medical staff committees should review protocols in the developmental stage, and a one-on-one conference should be conducted with key stakeholders to foster the support needed for implementation. An understanding of the medical center environment, medical staff objectives, and incentives for change can assist in developing a strategy to gain medical staff support of protocols.

Many barriers are encountered during implementation of complex programs such as these. Despite known benefits of protocol-driven care, therapists can view them as too much work and physicians can perceive them as loss of control over the patient. Such barriers need to be addressed and can be overcome through education, participation, and sharing in the positive outcomes of the program. Establishing a high level of support and intrinsic motivation among respiratory care staff is the most important aspect of implementation and can also be the most difficult, particularly in a program that demands that the therapists learn new skills, enhance communication abilities, and adapt to change. Workgroups and teams consisting of members of the department can accelerate planning and implementation.

The adage, "the best evidence of life is growth," is particularly true for respiratory care protocols. To be effective and to reflect the true state-of-the-art in therapy, the protocols must be regularly reappraised. The protocols must be routinely updated as new medical information relevant to respiratory care becomes available. In addition, routine feedback from physicians and other staff members during protocol updating helps to ensure that the protocols remain practical and fosters communication with the entire healthcare team.

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    This issue is an excellent compendium of information, including the rationale for protocols, the logistics for implementing them, and legal considerations.

VI. CARDIOVASCULAR AND THROMBOEMBOLIC DISEASE

63. THROMBOEMBOLIC DISEASE: EPIDEMIOLOGY, NATURAL HISTORY, AND DIAGNOSIS

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Venous thromboembolism (VTE) is, in theory, an entirely preventable or treatable disease. Yet, it is a persistent and prevalent cause of morbidity and mortality responsible for an estimated 50,000 death and 500,000 nonfatal episodes each year in the United States. Important diagnostic and therapeutic developments have occurred in the past decade, but medical science is only at the beginning of the path to understanding this disease. Consequently, clinical strategies, as yet, have only partially achieved the goal of preventing disability and death from it.

By definition, VTE originates in systemic venous thrombosis, and is pathologically distinct from arterial thrombosis. Conditions that favor thrombosis can be grouped into three categories, as predicted by Virchow more than a century ago: (1) venous stasis; (2) injury to the venous intima; and (3) alterations in the coagulation-fibrinolytic system. The potential role of all three factors has been demonstrated in a variety of situations. Venous stasis occurring during hospital bedrest is associated with deep venous thrombosis (DVT); using intermittent compression stockings to restore venous flow reduces the risk for DVT. Injury to the venous wall is the most likely mechanism of the many lower extremity DVTs observed in proximity to sites of trauma and major orthopedic surgery. Coagulation abnormalities that occur alone or in concert with other conditions can promote clinical venous thrombosis. For example, an increased risk is seen for VTE associated with mutations in factor V (Factor V_{Leiden}) and in the untranslated region of the gene encoding prothrombin (although the procoagulant mechanism of the latter mutation is still under investigation). Other less prevalent, but probably more potent, *thrombophilias* include deficiencies of antithrombin III, protein C, and protein S; aberrations in the thrombolytic system; and the presence of the doubly misnamed *lupus anticoagulant*. Clinical conditions that entail combinations of these fundamental risk factors are associated with a higher risk of thrombosis.

Many large studies have identified the major risk factors for DVT of the lower extremities. These include (1) surgery involving general anesthesia for more than 30 minutes; (2) injury or surgery involving the lower extremities or pelvis; (3) congestive heart failure; (4) any cause of prolonged immobility; and (5) pregnancy, particularly during the postpartum period. Other factors that increase risk are cancer, obesity, advancing age, varicose veins, a prior episode of DVT, the use of estrogen-containing compounds, and dehydration. Predictably, these risk factors are cumulative.

Investigations clearly indicate that the deep veins of the lower extremities are the dominant source of clinically significant pulmonary emboli—an important epidemiologic, diagnostic, and therapeutic point. Less commonly, thrombi can arise in superficial veins and in prostatic, uterine, renal, and other veins. They can also occur in the right cardiac chambers in patients with right ventricular failure. However, more than 95% of clinically significant pulmonary emboli arise from DVT in the lower extremities (whether or not such DVT is clinically detectable).

The events initiating venous thrombosis are not fully understood. Clearly, the valves of the lower extremity veins, especially in the calves, are common sites for the initial event. The development of a small nidus leads to the elaboration of clot-potentiating materials that trigger prolongation of the thrombus with red blood cells (RBCs), fibrin, and, to a lesser degree, platelets. Once formed, the thrombus grows by accumulating additional RBC, fibrin, and platelet *layers*, seen pathologically as the *lines of Zahn*.

Even as thrombosis is occurring, the process of resolution is initiating. The thrombi resolve by one or both of two mechanisms: fibrinolysis and organization. Fibrinolysis refers to actual dissolution of the thrombus by plasma enzymes. It is a relatively rapid process, proceeding over a period of hours to several days. If fibrinolysis is not totally

successful, organization finishes the job of resolution. Reparative cells infiltrate the residual thrombus and replace the *thrombotic components* with connective tissue. The fibrotic residuum is then incorporated into the venous wall and re-endothelialized. Organization usually thickens the venous wall, which can provide loci for further thrombus formation. The thickening can also incorporate one or more venous valves, rendering them incompetent. Whatever the fate of a given thrombus, available data indicate that the sequence of resolution is complete within 7 to 10 days. By that time, the initial thrombus is gone or has been incorporated into the venous wall. In the latter case, the pathology is more accurately termed a *venous scar* than an *old clot*.

At any time during the process of resolution, a pulmonary embolism can occur. It is important to recognize that embolism is not a disorder *per se*; it is merely a complication of DVT. Because thrombi are most friable early in their development, embolic risk is greatest during the first few days after thrombus formation. Thereafter, dissolution or organization sharply limits embolic risk (as long as no new thrombotic material has been laid down in the interval).

When emboli arise and lodge in one or more pulmonary arteries, hemodynamic and respiratory consequences occur. The hemodynamic consequences include a decrease in the available cross-sectional area of the pulmonary arterial system through both mechanical obstruction and release of vasoconstrictive thrombus metabolites directly into the vascular bed. The pulmonary vascular resistance rises, causing an increased pulmonary arterial pressure, and, therefore, an increased right ventricular workload. If these consequences are severe, the right ventricle may not tolerate the workload and the cardiac output will fall. Respiratory consequences include (1) altered ventilation-perfusion relationships, which (combined with a fall in cardiac output and resulting lowered venous oxygen concentration) can lead to arterial hypoxemia; (2) development of one or more zones of alveolar dead space (zones that are ventilated but not perfused); (3) transient pneumoconstriction of these same zones; (4) hyperventilation (the reasons for which are debated); and (5) loss of surfactant in the underperfused zones. The first four events occur immediately; the fifth requires approximately 24 hours of total occlusion before alveolar surfactant is depleted. The two major consequences of surfactant depletion are atelectasis and an increase in permeability of the alveolocapillary membrane, causing further problems with gas exchange.

One consequence of embolism—pulmonary infarction—is rare. Less than 10% of emboli lead to infarction. Therefore, embolism is by no means synonymous with infarction.

An important clinical question concerns the hemodynamic deterioration observed in some patients with pulmonary embolism in the first few days after embolization. Although pulmonary embolism can be immediately fatal, a large number of patients who eventually succumb do so 1 or more days after presentation. It stands to reason that these *late fatalities* are caused by either progressively deteriorating myocardial fatigue (i.e., right ventricular infarction or other myocyte injury) or increases in workload because of factors such as recurrent emboli, embolus propagation, or further release of vasoactive mediators from the embolus.

One aspect of embolism has become more widely recognized since cardiac echocardiography has been more extensively used; namely, that some embolic fragments may be entrapped in the right atrium or ventricle, whereas others reach the pulmonary vasculature. These events—embolic fragmentation and retention in the right cardiac chambers—have long been recognized in experimental embolism. The clinical significance of these sessile cardiac thrombi has not been studied in a controlled fashion. However, it stands to reason that these thrombi are highly likely to embolize, and larger cardiac thrombi may warrant emergent invasive removal, especially in the presence of pre-existing hemodynamic compromise.

Beyond these acute events, emboli (as with venous thrombi) tend to resolve if prevented from propagating by anticoagulants. Precise data on the speed of resolution in humans are not available. The earliest reported time of total embolic resolution is approximately 2 days; most resolve substantially or completely within a few weeks. A very small number (perhaps <1%) fail to resolve, for unknown reasons.

Signs and symptoms of DVT are inconsistent; they are essentially manifestations of its two consequences: inflammation of the venous wall and venous obstruction. The former can lead to local pain, tenderness (tenderness along the vessel wall is particularly

suggestive), redness, and warmth; the latter can lead to edema in the leg zones drained by the vein(s) involved. Unfortunately, studies have demonstrated that less than half of patients with DVT have signs or symptoms at all and few have sufficient inflammation or edema to allow a clinical diagnosis to be made. Therefore, reliable and early detection requires that laboratory tests be used to supplement history and physical examination.

Three well-validated diagnostic procedures are generally available to diagnose and follow the course of DVT: compression ultrasound, impedance plethysmography (IPG), and contrast venography. Radiolabeled fibrinogen, a previously invaluable investigative tool for detecting thrombus presence and propagation, is no longer available. Other tests, such as serological markers of thrombosis or thrombolysis, magnetic resonance imaging (MRI), and radiolabeled thrombus-specific agents, are under development, but have not been completely validated for clinical use.

Compression ultrasonsography involves the use of ultrasound visualization and Doppler analysis to distinguish between solid (thrombus) and fluid (blood) contents of the proximal deep veins of the leg. Failure to compress visualized veins suggests that at least part of the lumen is filled with solid material and is the only reliable criterion for DVT diagnosis. Findings such as *echogenic densities* or Doppler blood flow velocity measurements have not proved reliable in clinical studies and should not be used to make the diagnosis. The technique is not reliable in detecting thrombi limited to the calf or iliac veins. In addition, the vessel wall thickening from prior DVTs causes wall thickening in nearly half of cases, which can cause noncompressibility on ultrasound. Even the most rigorously controlled clinical trials, using complex algorithms to compare old and new studies side-by-side, distinguished new thrombi from old scars only with great difficulty. In its current state, compression ultrasonsography should not be used to diagnose recurrent DVT at the site of prior thrombosis.

Impedance phlethysmography, which measures the rate of venous drainage from the leg, is positive when substantial obstruction occurs to venous outflow at any point from the popliteal vein to the inferior vena cava. It is sensitive to thrombi above the knee, especially when unilaterally positive. The test has been well validated in clinical studies and is a relatively inexpensive, standardized method to detect DVT. A great deal of work has been performed comparing the accuracy of IPG with that of compression ultrasound. As a group, these studies show compression ultrasound to be slightly more accurate, although it is more expensive and highly user-dependent. Our preference on a cost and convenience basis is to use the IPG test first, and ultrasound only if the IPG results are equivocal or inconsistent with our clinical suspicions. Unlike ultrasound, IPG has the additional benefit of returning to normal within weeks of an acute DVT, making it useful for diagnosing DVT recurrence. It should be noted that neither of these two noninvasive tests reliably detects calf thrombi or asymptomatic proximal vein thrombi.

Contrast venography is an invasive test in which radio-opaque contrast is injected into the leg veins, yielding a very complete image of leg DVTs on radiographs, even in the calves. However, it has substantial drawbacks, including expense and discomfort. Currently, contrast venography is usually reserved for special situations, such as patients suspected of having recurrent DVT, those with equivocal results on IPG or ultrasound testing, or those in whom those tests cannot be done (e.g., those with extensive lower extremity trauma or casts).

Among the promising newer techniques for DVT diagnosis are serological tests of thrombosis (fibrinopeptide A and B, prothrombin fragment F1+2, thrombin-antithrombin complexes, and soluble fibrin monomer) or thrombolysis (D-dimer). A potential advantage of these blood tests is that their results may correlate with the presence of both DVT and pulmonary embolism. At present, these tests are still under investigation. The D-dimer assay is the only one that has been extensively evaluated clinically, but it suffers from two drawbacks. The first is practical: only carefully performed, precise methods to measure D-dimers can distinguish normal controls from VTE patients, who may have only modestly elevated plasma levels. Second, even when D-dimers are measured using sophisticated enzyme-linked immunoassays, the plasma elevations are so common in medical illnesses that relatively few hospitalized patients have normal values for this assay!

Magnetic resonance imaging (MRI) has been explored as a diagnostic tool for DVT. The results of initial studies performed by investigators at specialized centers have been

encouraging, and suggest that the technique could be used to diagnose both DVT and pulmonary embolism, and perhaps even distinguish new DVTs from old venous scars. These reports, however, are preliminary and must be interpreted with caution. Large trials comparing MRI results with standard venography have not been performed, nor have outcome studies verified the safety of managing patients based on MRI results. Another consideration is that the interpretative performance of the expert readers who are pioneering this new technology may not be easily matched in general practice.

Radiolabeled thrombus-specific agents, such as antibodies targeted at components of fibrin and platelets, are under investigation. When these agents are systemically injected, they bind to acute thrombi and localize them as *hot spots* on nuclear medicine scans. As with MRI, these scans have the potential for diagnosing both pulmonary embolism and DVT simultaneously. Furthermore, because they are specific for the biochemical components of acute thrombi, they do not bind to venous scars and may distinguish them from recurrent DVTs. Finally, agents specific for propagating thrombi may foster unique insights about the ability of different anticoagulant drugs to *extinguish* active clotting.

As is true for DVT, clinical data are not sufficient to confirm or exclude the diagnosis of pulmonary embolism. This fact notwithstanding, the recognition of signs and symptoms suggestive of pulmonary embolism is the single most important factor in preventing death from this disease. This point is highlighted by the rather chilling observation that, in the vast majority of patients who die with pulmonary embolism, the condition was not diagnosed or even suspected ante mortem. Furthermore, although few patients who succumb to pulmonary emboli manifest all of the *textbook* clinical clues, almost all manifested at least one of them. The clinical impact of sophisticated diagnostic technology in reducing fatality from pulmonary embolism pales in comparison with the role of the astute clinician who maintains a low threshold for suspicion.

Signs and symptoms (even nonspecific ones) unexplained by other pathology should raise the possibility of pulmonary embolism and trigger a workup. Dyspnea of sudden onset is a nonspecific, but common symptom. Pleuritic chest pain and hemoptysis, which indicate infarction, occur in a few patients. Other individual symptoms (e.g., syncope and substernal chest pain) are even less common and suggest myocardial damage or strain. In addition, specific physical findings are usually few. Tachycardia of variable duration is also nonspecific, but is observed in most patients with pulmonary embolism. Other cardiac findings (e.g., increased pulmonic valve closure sound, right ventricular S_3, and right ventricular tap) can be subtle and typically occur only in the (fortunately) rare cases of massive embolism. Examination of the lungs rarely discloses a pleural friction rub or evidence of pleural effusion because these require infarction. Scattered rales or focal wheezing may be heard but are hardly diagnostic.

Clinical clues are vitally important for suggesting the diagnosis of pulmonary embolism, but as is true for DVT, objective testing is necessary to confirm or refute it. Unfortunately, *routine* tests cannot offer such confirmation. The arterial P_{O_2} is variable and a low value is commonly observed in other respiratory disorders. The chest x-ray study is most often either normal or discloses nonspecific findings such as small pleural effusions. The electrocardiogram commonly shows only sinus tachycardia. Although such tests may be highly suggestive and are useful in ruling out other diagnoses (e.g., pneumothorax, myocardial infarction), a definitive diagnosis of pulmonary embolism can be arrived at only through a limited number of specific tests.

The currently available diagnostic techniques—ventilation and perfusion scintiphotography, computer-assisted tomography (CT) scanning and MRI, DVT studies, and pulmonary angiography—all have potential roles in the workup for pulmonary embolism. Each test has, in turn, been declared the *optimal study*; however, each has its own specific values and limitations. It is better to individualize the choice and interpretation of these complementary imaging studies to the particular clinical situation. Unfortunately, blood tests are not yet capable of diagnosing pulmonary embolism in clinical practice.

The pulmonary perfusion scan is highly sensitive, but nonspecific; it is recommended as the first test for most patients suspected of having a pulmonary embolism. A negative scan is invaluable because it rules out the diagnosis as reliably as a pulmonary angiogram; however, a positive scan can be caused by many disorders other than embolism. Combining perfusion lung scans with ventilation scans, chest x-ray study, or both enhances the specificity of the procedure. Embolism is most reliably diagnosed

in cases of segmental or larger perfusion defects (which are normally ventilated) in the presence of a clear chest x-ray finding. Defects anatomically *matched* by radiographic opacities or ventilation defects should be regarded as nondiagnostic and should prompt further workup. Smaller perfusion defects occur less commonly with pulmonary embolism, but these scan findings, regardless of ventilation results, should be regarded as nondiagnostic. Using *probability* estimates to make treatment decisions, by definition, is a gamble. Careful consideration of the risks of an incorrect diagnosis should guide the decision to continue the workup.

If the diagnosis of pulmonary embolism is in doubt after noninvasive testing, searching for DVT is a sensible strategy. Because the two diagnoses are manifestations of the same disease, the treatments are largely the same. The yield of noninvasive testing for DVT is low (<10%) in patients with pulmonary embolism without leg symptoms. However, the potential benefits of making the diagnosis without further thoracic imaging justifies the performance of noninvasive leg testing, even in patients without leg symptoms.

Cross-sectional tomographic imaging of the thorax, using either CT or MRI, is under investigation as a diagnostic tool for pulmonary embolism. Both techniques make use of intravascular contrast to fill the lumen of the pulmonary arteries. (Unfortunately, the initial optimism that noncontrast MRI would distinguish thromboemboli based on their specific signal characteristics did not come to fruition.) Currently, CT scanning has the advantages over MRI of higher special resolution, wider availability, and larger clinical series demonstrating its value. Both technologies, however, are constantly advancing and the diagnostic value of each test is likely to improve. In both types of scans, emboli are detected as focal defects in pulmonary artery filling. Both scans, when performed and interpreted correctly, are capable of identifying emboli in the segmental or larger pulmonary arteries. However, certain areas, such as the hila, are susceptible to false-positive findings. Reading emboli in these areas should be done with special care. Perhaps more importantly, neither scan is of much value in imaging emboli in subsegmental pulmonary arteries. Insufficient data exist to support the notion that thromboembolic disease invisible to thoracic tomography does not require treatment. Until this decision can be guided by carefully designed clinical trials, a negative thoracic CT scan or MRI does not indicate that withholding treatment is safe. Negative scans should be followed up with further testing.

If other tests to confirm or refute the suspicion of pulmonary embolism are nondiagnostic, angiography may be indicated. Pulmonary angiography remains the *gold standard* because it can demonstrate the embolus itself, even in subsegmental pulmonary arteries. The procedure is invasive, but can be performed with little risk if special care is exercised. The most common serious complications arise from the use of contrast dye—the same amount of contrast dye used for helical CT scanning. The quality of the angiogram and the experience of the interpreter condition the diagnostic value of angiography. The decision to perform angiography in patients with equivocal results from noninvasive studies must be based on the specific clinical situation. The fundamental rule is *the greater the risk involved in making a therapeutic decision, the higher the degree of diagnostic certainty required.* The small risk involved with angiography in these patients is minor in comparison with the risks involved with making the wrong diagnosis: unnecessary long-term anticoagulation or, conversely, complications of untreated thromboembolism. It must be kept in mind, however, that if DVT has been diagnosed, it is rarely necessary to proceed to angiography because the need to treat the patient already has been established and—except in rare instances—the treatment regimen is the same.

New procedures to diagnose pulmonary embolism are generally the same as those discussed for DVT, including the use of ^{111}In platelets, radiolabeled monoclonal antibodies directed against other embolic components, CT, and MRI. These agents are still under investigation and their diagnostic value remains to be defined.

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64. THROMBOEMBOLIC DISEASE: PROPHYLAXIS

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The best way to reduce the morbidity and mortality associated with venous thromboembolic disease (VTE) is to prevent it from occurring in the first place. When performed properly, the risks of VTE prophylaxis are small and the potential benefits are enormous. It is clear that the informed use of VTE prophylaxis can substantially reduce the incidence of death and disability from this disease. The ultimate goal—

safely preventing VTE entirely—which has not yet been achieved, is the focus of a great deal of basic and clinical research.

Theoretically, two options exist: (1) to provide prophylaxis for VTE; or (2) to monitor with noninvasive tests and treat if VTE develops. In virtually all patients, the first option is the best because venous thrombosis and embolism can develop rapidly, and the first signal of these events can be a sudden, fatal embolic event.

Strategies to prevent VTE must address the mechanisms behind how venous thrombi are formed and how they progress to clinically significant disease. The basic science underlying the pathogenesis and natural history of VTE is only partially understood, a fact that is reflected in our inability to prevent this disease. In addition, clinical studies to evaluate prophylactic methods suffer from an incomplete understanding of how best to define and detect *clinically significant VTE*. These considerations notwithstanding, the prophylactic methods developed and validated thus far have had a tremendous impact on the incidence of this disease.

Deep venous thrombosis (DVT) and pulmonary embolism are best thought of as different manifestations of VTE, rather than as separate disorders. The vast majority (>95%) of clinically significant pulmonary emboli arise from deep veins of the lower extremities. Thus, the prevention of pulmonary embolism, for the most part, is really the prevention of lower extremity DVT. Substantial data now exist indicating that only the lower extremity DVTs extending into the proximal deep veins (popliteal and above) cause clinically apparent emboli; thrombi that remain confined to calf veins pose no significant embolic risk.

It is not known whether this observation reflects the fact that thrombi restricted to the calf veins do not embolize or that emboli from them are so small that clinical disease does not result, although the latter is more likely. Whatever the case, it is now evident that the key to preventing pulmonary embolism is the prevention of DVT of the lower extremity veins or, failing this, prevention of the extension of calf vein thrombosis into the more proximal venous system.

Two requirements to develop an effective strategy for preventing any disorder include (1) identification of the patients at risk; and (2) the availability of effective prophylactic modalities. For DVT, both of these requirements have been largely, but incompletely satisfied. The risk associated with various patient populations has been well defined, yet an accurate method of assessing the risk for individual patients is lacking. Likewise, the efficacy and safety of several prophylactic regimens have been established clinically, although these trials are complicated by the difficulties inherent to detecting asymptomatic DVT and controversies over its clinical importance.

The decision to apply prophylaxis involves a weighing of the risk of venous thrombosis (and, therefore, pulmonary embolism) versus the risk of the prophylactic regimen. The risk factors are cumulative and the total clinical picture mandates both the presence and the intensity of prophylaxis. For example, patients undergoing extensive lower extremity orthopedic surgery are at very high risk for DVT, and require aggressive mechanical and moderate-dose anticoagulant prophylaxis. Younger, healthier persons with less severe medical problems and limited immobilization could receive adequate prophylaxis with lower doses of anticoagulants or mechanical methods alone.

Several mechanical and pharmacologic methods are used to prevent VTE. The exact prophylactic *recipe* appropriate for each particular risk group is beyond the scope of this chapter and is periodically reviewed elsewhere. What follows is a discussion of the available methods and general comments regarding applicability. In this respect, many studies have been performed to compare different methods or drug regimens for VTE prophylaxis. Although these trials can provide useful clinical guidance, they should be interpreted with some care: consider each trial's sponsorship and scientific rigor and note whether the comparative medication is given in optimal doses, or, for mechanical modalities, whether the optimal devices or methods are used.

The mechanical compressive devices inflate a cuff for several seconds each minute, which prevents venous stasis. Some compress the calf alone; others, the calf and thigh sequentially. Little efficacy difference appears to be seen between the two. Although it is presently unknown whether different pressures and speeds of intermittent cuff inflation will lead to improved prophylactic efficacy, it is clear that the pattern of rhythmic inflation is helpful, because simple elastic stockings have not been shown to

be useful (unless patient-tailored to provide a gradient of pressures). The intermittent compressive devices are safe, effective, and well tolerated. The only contraindications to their use are the presence of active venous thrombosis, which should be ruled out before their application if such is suspected; limb ischemia caused by arterial insufficiency; or circumstances that prevent their application (e.g., a cast in place). The devices should be applied promptly (e.g., preoperatively) and maintained during the risk period. This approach has particular value in those patient groups for whom antithrombotic drugs are contraindicated (e.g., neurosurgical, head trauma, known hemorrhagic diathesis).

Prophylactic subcutaneous heparin has been widely studied. Given in doses of 5000 to 7500 U subcutaneously every 8 to 12 hours, it has proved a safe, efficacious preventive approach to DVT in most patient populations. This regimen is effective because of the inhibition of events that occur early in the coagulation cascade, before the elaboration of thrombin. After initial screening studies (e.g., platelet count, partial thromboplastin time, prothrombin time, careful history), no further coagulation studies are necessary to monitor the patient. Substantial experience has indicated that a low bleeding risk is associated with this regimen, even in surgical populations.

Low molecular weight heparins (LMWH), a heterogeneous group of drugs derived by partial depolymerization of heparin, present another option for prophylaxis. As with heparin, they are administered subcutaneously for DVT prophylaxis. They possess certain theoretic advantages over (unfractionated) heparin, such as more predictable pharmacokinetics, allowing dose escalation without laboratory monitoring; and a reduced incidence of laboratory-demonstrated, heparin-induced thrombocytopenia during routine use. These medications are ten times more expensive to use than heparin and would constitute a great increase in pharmaceutical cost if adopted for all prophylactic needs. The high cost of the various LMWHs will be justified if each drug represents a true clinical advantage over *properly dosed* heparin.

Warfarin is an alternative effective drug for prophylaxis in patients at high risk. Several regimens have been studied, particularly in very high-risk groups (e.g., hip replacement). One approach is to begin before surgery with low doses (1–2 mg/d), then escalate to a therapeutic range after surgery. Another is to begin warfarin only after surgery, finally achieving the desired prothrombin range (International Normalized Ratio of 2.0–3.0) after several days. It is likely that these regimens do not prevent small calf thrombi but do prevent extension into the popliteal veins and above, thereby sharply reducing embolic risk.

Hirudin, a potent thrombin inactivator, has been studied under several clinical conditions for DVT prophylaxis. Results of initial clinical trials have been encouraging for its use in both prophylaxis and treatment of VTE. Further studies must be performed before it can be recommended for clinical use.

Among other options, aspirin, dipyridamole, sulfinpyrazone, and other *antiplatelet* drugs have not been shown to be useful for prophylaxis of venous thrombosis. Reports regarding the value of intravenous infusion of low molecular weight dextran are mixed, placing this polymer in the category of *probably effective*. Dextran does carry the potential risk of volume overload and allergic reactions.

In some patients at high risk, neither antithrombotic agents nor venous compression devices can be applied (e.g., patients with extensive trauma). In such patients, prophylactic placement of an inferior vena caval filter should be considered.

The prophylactic approach selected depends on the magnitude of thromboembolic risk and the relative risks inherent to prophylactic methods. In patients at low or moderate risk, either the application of intermittent pneumatic leg compression devices or prophylactic doses of subcutaneous low-dose heparin or warfarin will provide adequate protection. Such patients include those who are immobilized for brief periods, are undergoing general surgical procedures (e.g., cholecystectomy), or have suffered an uncomplicated myocardial infarction. However, none of these individual approaches provides optimal protection in patients at high risk: patients with trauma to the pelvis or lower extremities; patients undergoing extensive surgical procedures on the lower extremities (e.g., hip or knee replacement) or surgical prostatectomy; and patients with multiple risk factors. In these individuals, multiple studies have indicated that the combination of intermittent leg compression with either heparin or warfarin provides optimal protection.

Regardless of the specific regimen selected, it is clear that prophylaxis now can, and should, be applied to all patients at risk of venous thromboembolism. Failure to apply prophylaxis should be specifically justified. Because prevention of DVT is the best means of preventing pulmonary embolism and death caused by embolism, and because most venous thrombi arise among hospitalized patients to whom a prophylactic option easily can be applied, widespread use of prophylactic options can currently considerably reduce the incidence of DVT and pulmonary embolism. Further developments in this field hold the promise of safely preventing DVT and pulmonary embolism even further, perhaps to the point of eliminating them entirely.

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65. THROMBOEMBOLIC DISEASE: THERAPY

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Rational management of venous thromboembolism (VTE) must be guided by the goals of treatment. The clinical goals are to prevent or minimize serious sequelae from both deep venous thrombosis (DVT) and pulmonary embolism, including (1) death from pulmonary embolism; (2) dyspnea, chest pain, and hemodynamic instability from pulmonary embolism; (3) leg discomfort from thrombotic occlusion of the deep veins; (4) long-term recurrence of VTE; and (5) other long-term problems such as postphlebitic leg swelling and pulmonary hypertension. From a biological perspective, the goals of therapy in the acute setting are to reduce the amount of vascular obstruction from pulmonary embolism and DVT, as well as prevent embolization (or further embolization) of DVT. In the case of hemodynamically significant pulmonary embolism, it may also be important to inhibit the release of vasoactive substances into the pulmonary circulation and optimize right ventricular function. Although the biological mechanisms relevant to the long-term goals of therapy are incompletely understood, factors such as reducing the damage to the venous wall and valves are likely to be important.

In most cases, the treatment of both DVT and stable pulmonary embolism are identical. The treatment of choice in the acute phase is heparin or, in some situations, low molecular weight heparins (LMWH). Although the mechanisms of action are somewhat different, both heparin and LMWH catalyze endogenous antithrombin III to stop ongoing thrombosis directly. These drugs are the only widely available agents that immediately inhibit growth of both DVT and pulmonary embolism. By halting thrombus growth, they allow the action of the fibrinolytic system to proceed unopposed. Thus, they indirectly speed the resolution of pre-existing DVT and pulmonary embolism and reduce the size of potential emboli. Clinical evidence suggests that some LMWH are equal to heparin in safety and in efficacy. The choice between agents depends in large part on their relative cost and ease of administration.

Neither heparin nor LMWH reduces embolic risk or enhances thrombus resolution directly. Treated patients remain at embolic risk until their DVTs have either dissolved or become organized. Thus, embolization occurring in the first few days of therapy does not reflect *drug failure*. Only thrombus growth or initiation of a new thrombus during therapy is evidence of heparin (or LMWH) failure. Furthermore, some 50% of patients with above-knee, acute DVT already have had asymptomatic pulmonary emboli. It is important not to mistake the subsequent discovery of these pre-existing emboli for evidence of recurrent thromboembolic disease.

The need to treat lower extremity DVT appears confined to those patients with involvement of the popliteal vein and above; thrombosis that remains confined to the calf veins does not require anticoagulant therapy. Both compression ultrasound and impedance plethysmography (IPG) are convenient, reliable ways to make this distinction. However, if IPG or ultrasound is not available or if the patient cannot be followed by reliable tests (for 10–14 days) to ensure that extension of calf-limited thrombi does not occur (as it does in 15% to 20% of cases), patients with calf-limited thrombi should be treated. Because serial outpatient testing over the course of a week avoids hospitalization, this is a useful, cost-effective approach; but a system must be in place for such follow-up if this option is adopted.

Two heparin regimens are commonly used in the treatment of VTE: continuous intravenous infusion of approximately 18 U/kg/h or twice daily subcutaneous injections of approximately 250 U/kg. Over the years, studies favoring one or the other of these regimens have appeared; the issue of which regimen is safest, most effective, or both, remains unresolved. Unquestionably, the continuous intravenous regimen has been the most popular. The subcutaneous route allows more mobility and possible outpatient management, and so may gain popularity in the current era of medical cost-containment.

The best method for laboratory monitoring of heparin therapy and the necessity for such monitoring remain controversial issues. Current laboratory tests do not reliably predict a safe or effective heparin dosage regimen. It is well known that the results of these tests can vary widely from laboratory to laboratory, depending on the technical details of sample handling, reagents, and test performance. Furthermore, substantial diurnal variation can occur in tests obtained during continuous intravenous infusion of heparin, so that an 8 a.m. test does not reliably predict results some hours later. This applies to the three most widely used tests: whole blood clotting time, plasma recalcification time, and activated partial thromboplastin time (aPTT). The last test is the most popular one; the general wisdom is that the aPTT should be maintained at 1.5 to 2.5 times control during continuous intravenous infusion, and it should be 1.5 times control just before the next dose on an intermittent schedule. Although animal and clinical studies suggest that continuous prolongation of the aPTT above 1.5 times control is associated with less thrombus growth and VTE recurrence, the observed effects may be caused entirely by the use of appropriate doses of heparin (outlined above), irrespective of the aPTT test results. Indeed, a meta-analysis has indicated that subcutaneous regimens, with or without monitoring, are at best as safe and effective as intravenous regimens; other studies have noted the vagaries of the aPTT for monitoring therapy.

The major complication of therapy with heparin or LMWH is hemorrhage. The initial hope that LMWH would be safer than heparin was not borne out in clinical studies; both drugs most likely carry the same risk of bleeding. In fact, factors other than the type and dose of heparin appear to be far more important in determining bleeding risk, including age (especially beyond the sixth decade); the presence of unsuspected or known bleeding sites (e.g., stomach, bowel, kidney); uremia; and demonstrable hemostatic defects (e.g., thrombocytopenia). Available data indicate that bleeding risk is very low among patients who do not have a significant coexistent disease or coagulopathy. It should also be noted that many hemorrhagic episodes in heparinized patients occur when clotting parameters are in *therapeutic range* and in the absence of any identifiable risk of hemorrhage.

The necessary duration of anticoagulant therapy for VTE is controversial, both in the acute stage and in follow-up. In the acute stage, thrombi contain a high concentration of activated clotting factors and direct inhibition with heparin or LMWH is necessary to halt the thrombotic process. Although clinical data are relatively sparse, most experts agree that at least 5 days of heparin or LMWH are necessary for initial treatment. The limited available evidence indicates that venous thrombi resolve or become organized approximately within this timeframe.

Follow-up anticoagulation therapy is necessary in almost all cases to prevent recurrence of VTE. The appropriate type and duration of therapy should be tailored to the clinical situation. Patients at high risk for recurrence, characterized by having unresolved risk factors for VTE, are likely to require prolonged (possibly lifelong) anticoagulation. In some cases, persistent risk factors reflect chronic conditions such as immobility, heart failure, or persistent venous obstruction. In addition, patients with *idiopathic* VTE have high rates of recurrence and are likely to have persistent *hypercoagulable states*, based on either known biochemical disorders or on as yet uncharacterized factors. The duration of follow-up anticoagulation necessary for patients with transient risk factors is controversial. The simple clinical answer is that protection should be continued until the original risk factor(s) have subsided (e.g., the broken leg has healed and the patient is fully ambulatory). Most experts, however, recommend at least 6 months of anticoagulation therapy for patients with VTE, even those with transient risk factors.

As soon as the diagnosis of VTE is confirmed, assume that follow-up treatment will be required beyond hospitalization. Currently, warfarin is the most practical option; it can be initiated as soon as heparin has been started. Heparin is continued until the pro-

thrombin time has been in range (International Normalized Ratio: 2.0–3.0) for 2 consecutive days. At that point, heparin can be discontinued and the patient discharged on warfarin. If, for some reason, warfarin cannot be used, high doses of subcutaneous heparin (adjusted to keep the aPTT < 1.5 × control) can be started on day 6 and the patient discharged on this regimen. Both approaches are acceptable; the choice involves the patient's desires (e.g., injections versus the need for regular prothrombin times).

Approaches specific for DVT therapy have been proposed, but are not commonly used. Surgery (e.g., thrombectomy, ligation) has no role. Current data do not indicate that available thrombolytic agents (streptokinase, urokinase, tissue plasminogen activator) offer improved short- or long-term outcome (versus heparin) in patients with DVT, and increase the risk of intracranial hemorrhage. Future studies with new or existing thrombolytic agents may modify these views.

Although the treatment of pulmonary embolism in very stable patients is generally identical to that for DVT, several facts specific to pulmonary embolism treatment deserve consideration. The most important issue is that outpatient, subcutaneous treatment regimens have only been tested on the most clinically stable patients with pulmonary embolism. Less *healthy* patients merit hospital admission. Additional therapeutic issues specific to pulmonary embolism must be considered, including (1) the size of the initial dose of heparin and the dosage regimen during the first 24 hours; (2) the need for cardiopulmonary supportive measures; (3) the role of caval filters and surgery; and (4) the role of thrombolytic agents.

The size of the initial heparin dose required during pulmonary embolism is controversial. Animal data indicate that pharmacologically active peptides are released from platelets coating an embolus and that they contribute to the initial severity of the cardiopulmonary symptoms by inducing pulmonary vasoconstriction and bronchoconstriction. These studies have shown that a large initial bolus of heparin is necessary to inhibit platelet aggregation, which initiates release of these agents. Based on these data, I recommend a large initial intravenous bolus (15,000–20,000 U) of heparin, followed by a continuous infusion similar to the intravenous DVT regimens. Dose adjustment is generally the same as for DVT, but with special attention to avoiding low doses or aPTT values during the first 1 to 2 days of therapy. Some clinicians prefer to use larger dose heparin infusions during the initial 24 hours after an embolic event. This preference is based on the results of coagulation tests and the concept that high levels of thrombin may persist during this period. We do not give larger doses during the first 24 hours. No studies are available comparing our approach with the *high-dose* approach.

Cardiopulmonary supportive measures may be indicated for pulmonary embolism treatment, including administration of oxygen if arterial hypoxemia is present. Systemic hypotension, if present, is usually caused by acute right ventricular ischemia and failure. Animal experiments suggest that an important mechanism of right ventricular ischemia is low myocardial perfusion pressure (coronary pressure–right ventricular pressure) occurring as the right ventricle *strains* to overcome massive pulmonary artery obstruction. For that reason, we prefer systemic vasoconstrictive agents (e.g, phenylephrine) to raise arterial pressure (and coronary pressure) during pulmonary embolism-associated shock.

Another mode of therapy arose from evidence that, during massive pulmonary embolism, death was often caused by additional embolization of lower limb DVT occurring while the patient was already hemodynamically compromised. Although multiple procedures are available to prevent recurrent embolism of lower limb DVTs, our current choice is limited to the insertion of a Greenfield (or similar) inferior vena caval filter. These devices are easy to insert, do not interfere with caval blood flow, and have an excellent (95%) record of long-term patency. For us, it is the *standard* against which other devices and approaches should be measured. We consider filter placement a life-saving procedure and recommend it in the setting of proved massive embolism when a recurrence may be fatal. Because heparin cannot prevent recurrence during the first several days, it is during this period that caval interruption should be considered.

The role of thrombolytic agents in the management of pulmonary embolism is unclear. Management decisions must be made on the basis of indirect information rather than by comparative clinical trials. Multiple studies have established that these agents promote more rapid embolic resolution than heparin alone. No positive effects on morbidity or

mortality have been demonstrated, however, nor has the ultimate degree of embolic resolution been any greater. Moreover, these agents are costly and carry significant risks. Such agents may have a role in the management of the patient with massive embolism and persistent hypotension. Even in this situation, however, patient selection is difficult and only physicians familiar with the drugs should use them.

Acute pulmonary embolectomy (by thoracotomy, suction catheter, or balloon catheter) is a procedure that is probably never warranted because medical therapy is so successful, patient selection so difficult, and the results of acute embolectomy so unimpressive. Conceivably, situations occur in which massive embolism fails to respond promptly to medical therapy, the diagnosis is certain, and immediate, expert surgical intervention is possible. However, the procedure carries a very high mortality rate. Although considerable controversy exists about which, if any, cases require embolectomy, I have not encountered such an instance in many years.

The use of lung scans in ruling out asymptomatic embolism in patients with above-knee DVT, and in the predischarge evaluation of patients with embolism, merits comment. Often, in patients with DVT, pleuritic chest pain or other embolic symptoms appear several days after admission, and a scan demonstrates defects. In my experience, these defects were usually present on the admission scan and, therefore, do not merit a change in therapy. Absent the admission scan, such decisions are much more difficult. The predischarge scan not only provides evidence of satisfactory embolic resolution but also alerts the physician to the possibility that the patient may require close follow-up to rule out chronic postembolic pulmonary hypertension (see Chapter 66).

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66. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Peter F. Fedullo

Under most circumstances, the natural history of acute pulmonary embolism involves either total resolution or resolution leaving minimal residua, with restoration of normal pulmonary hemodynamics, gas exchange, and exercise tolerance. Chronic thromboembolic pulmonary hypertension (CTEPH), which occurs in a minority of patients following acute embolism, represents an alternate natural history. Although

exact incidence figures are not available, it is likely, based on the number of embolic survivors and the number of patients referred for the procedure, that CTEPH occurs in no more than 0.1% of patients who experience an embolic event.

The basis for CTEPH has not been established. Despite extensive investigation, the only identifiable thrombophilic tendency has been the presence of antiphospholipid antibodies found in approximately 10% of patients. The prevalence of antithrombin III, protein C, or protein S deficiency appears to be no greater than in the general population. Preliminary evidence also suggests that activated protein C resistance is no more common in patients with CTEPH than in the general population, and no consistent defect in fibrinolytic activity has been identified.

It is possible that patients with chronic thromboembolic disease represent an uncommon segment of the normal spectrum of pulmonary embolic disease, in which endogenous fibrinolytic mechanisms are overcome by the age, extent, or location of the obstructing embolus. Failure of diagnosis and treatment at the time of the initial embolic event may have occurred in many of these patients; recent data confirm that a significant incidence of venous thrombosis and pulmonary embolism is overlooked in the population at large.

The diagnosis of CTEPH is usually not made until the degree of pulmonary hypertension is advanced. As a result, the exact hemodynamic evolution of the disease has not been fully established. However, the symptomatic history has been well described. A patient can carry on relatively normal activities following a pulmonary embolic event, whether clinically apparent or occult, even when extensive pulmonary vascular occlusion has occurred. Following this asymptomatic period, which can range from months to years, worsening exertional dyspnea, hypoxemia, and right ventricular failure ultimately ensue. The basis for this asymptomatic (*honeymoon*) period followed by gradual hemodynamic and symptomatic decline has only recently been elucidated.

The progressive nature of the pulmonary hypertension in most patients with chronic thromboembolic disease does not appear to be the result of recurrent embolic events or *in situ* thrombosis, as initially postulated. Most patients with sequential perfusion scans experience symptomatic and hemodynamic decline in the absence of new perfusion defects. As experience with the diagnosis and surgical management of this disease process has grown, it has become apparent that the increase in pulmonary artery pressures arises from two different sources: a decrease in the cross-sectional area of the pulmonary vascular bed associated with the unresolved thromboembolic component of the disease; and the development over time of a distal, small-vessel arteriopathy pathologically indistinct from that seen in a wide range of pulmonary hypertensive disorders. It appears that these secondary pulmonary hypertensive changes, perhaps induced by high pulmonary artery pressures or flows, result in an incremental increase in right ventricular afterload, progressive pulmonary hypertension, and, ultimately, right ventricular failure.

Progressive dyspnea is a complaint common to all patients with CTEPH. The subjective complaint of dyspnea must be considered in context of the patient's usual lifestyle. The sensation of dyspnea and development of exercise intolerance are more troubling and lead to earlier evaluation in patients who are normally active than in those who live a sedentary lifestyle. Later in the course of the disease, exertional chest pain, near syncope or syncope, and lower extremity edema can develop.

Although a history of documented thromboembolism may not be present, many patients can provide a history consistent with an acute embolic event. They may describe an episode of *pleurisy*, lower extremity *muscle strain*, or prolonged, atypical *pneumonia*. Alternatively, they may describe a hospitalization or surgical procedure from which they never fully recovered.

Diagnostic delay occurs commonly, particularly in the absence of an acute history of venous thromboembolism. Progressive dyspnea and exercise intolerance caused by CTEPH are often erroneously attributed to coronary artery disease, cardiomyopathy, interstitial lung disease, asthma, deconditioning, or psychogenic dyspnea. Before considering a pulmonary vascular problem as a basis for their complaints, many patients with CTEPH have undergone one or more left-sided cardiac catheterizations and coronary angiograms. Others have undergone lung biopsy. Still others have been advised to enroll in an exercise program or to seek psychiatric help. Unfortunately, the period of

diagnostic delay does not appear to have shortened substantially over the last several years, emphasizing that the status of the pulmonary vascular bed should be considered in any patient with dyspnea in whom no compelling cause for it can be established.

Findings on physical examination can be subtle early in the course of the illness, thereby contributing to the diagnostic delay. Before the development of significant right ventricular hypertrophy or overt right ventricular failure, abnormalities can be limited to a widened split of the second heart sound or a subtle accentuation of its pulmonic component. In time, obvious findings develop, which can include a right ventricular heave, jugular venous distention, prominent A and V wave venous pulsation, fixed splitting of S_2, a right ventricular S_4 or S_3, a murmur of tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema.

A distinctive physical finding in certain patients with chronic thromboembolic disease is the presence of flow murmurs over the lung fields. These subtle bruits, which appear to originate from turbulent flow through partially obstructed or recanalized pulmonary arteries, are high pitched and blowing in quality, heard over the lung fields rather than the precordium, accentuated during inspiration, and frequently heard only during periods of breath holding. Their importance lies in their not having been described in primary pulmonary hypertension, which represents the most common competing diagnostic possibility. These flow murmurs, however, are not unique to chronic thromboembolic disease; they can be encountered in congenital stenotic lesions of the pulmonary vasculature and in the pulmonary vasculitides.

The diagnostic sequence is relatively straightforward once an abnormality of the pulmonary vascular bed has been considered as a basis for the patient's complaints. Several goals of the diagnostic evaluation exist: (1) to establish the presence and degree of pulmonary hypertension; (2) to define its cause; and (3) if major vessel thromboembolic disease is present, to determine whether it is accessible to surgical intervention.

Findings on standard laboratory tests are nonspecific; they are dependent on the point in the natural history of the disease at which they are obtained and reflective of the hemodynamic and gas exchange consequences of the thromboembolic obstruction and the accompanying cardiac dysfunction.

The chest radiograph, although often appearing normal, may demonstrate one or more of the following findings that suggest the diagnosis: (1) enlargement of both main pulmonary arteries or asymmetry in the size of the central pulmonary arteries; (2) areas of hypoperfusion or hyperperfusion; (3) evidence of old pleural disease, unilaterally or bilaterally; and (4) evidence of right ventricular hypertrophy.

Pulmonary function testing is often within normal limits; however, approximately 20% of patients demonstrate a mild to moderate restrictive defect. A mild obstructive defect can be present as a result of mucosal hyperemia, which is related to the development of a large bronchial arterial collateral circulation. Most patients have a reduction in the single breath-diffusing capacity for carbon monoxide; a normal value, however, does not exclude the diagnosis. When a spirometric abnormality is present (reflecting either restrictive or obstructive disease), the degree of the abnormality is almost always less impressive than the patient's gas exchange abnormalities, symptomatic complaints, and degree of pulmonary hypertension.

Although the arterial P_{O_2} at rest may be within normal limits, the alveolar arterial oxygen gradient is typically widened and most patients have a decline in the arterial P_{O_2} with exercise. Dead space ventilation (V_D/V_T) is often increased at rest and worsens with exercise. Minute ventilation is typically elevated as a result of the increased V_D/V_T.

Echocardiography commonly provides the initial objective evidence for pulmonary hypertension. Findings include evidence of right atrial and right ventricular enlargement, abnormal septal position and motion related to the right ventricular pressure and volume overload, and evidence of pulmonary hypertension as determined from the tricuspid regurgitant jet.

Once the diagnosis of pulmonary hypertension has been established, it is essential to determine whether it originates from abnormalities of the small, resistance vessels or from central, chronic thromboembolic obstruction. Ventilation/perfusion lung scanning provides an excellent noninvasive means of distinguishing between potentially operable major vessel thromboembolic pulmonary hypertension and small vessel pulmonary hypertension. In chronic thromboembolic disease, at least one (and more commonly, sev-

eral) segmental or larger mismatched ventilation perfusion defects is present. In primary pulmonary hypertension, perfusion scans are either normal or exhibit a *mottled* appearance characterized by subsegmental defects. However, it is important to recognize that the ventilation perfusion scan often understates the actual extent of central pulmonary vascular obstruction from chronic thromboembolic disease. Channels through or partial flow around organized central obstructing lesions may allow the radioisotopic agent to reach the periphery of the lung. Depending on the distribution of flow, these areas can appear normal or as relatively hypoperfused *gray zones*. Ventilation perfusion scanning, therefore, can suggest the potential presence of chronic thromboembolic obstruction, but it cannot determine the magnitude, location, or proximal extent of the disease—information critical to the question of surgical accessibility.

Right ventricular catheterization and pulmonary angiography are essential to determine the degree of pulmonary hypertension, to exclude competing diagnoses, and to define the surgical accessibility of the obstructing thrombotic lesions. If hemodynamic measurements at rest demonstrate only modest degrees of pulmonary hypertension, measurements should be obtained following a short period of exercise. In patients with chronic thromboembolic obstruction sufficient to abolish normal compensatory mechanisms, exercise-related increases in cardiac output will be accompanied by an excessive elevation in pulmonary artery pressure.

The angiographic findings in chronic thromboembolic disease bear little resemblance to the sharply defined, intraluminal defects diagnostic of acute embolism. Five distinct angiographic patterns of pulmonary artery appearance have been described that correlate with the finding of organized thromboembolic material at the time of thromboendarterectomy: (1) central termination into a *pouch* configuration; (2) pulmonary artery webs or bands; (3) intimal irregularities; (4) abrupt narrowing of the major pulmonary arteries; and (5) obstruction of lobar or segmental vessels at their point of origin, with complete absence of blood flow to pulmonary segments normally perfused by those vessels.

One source of concern has been the safety of performing pulmonary angiography in patients with pulmonary hypertension. It has been proposed that the vasodilation induced by the contrast agent might induce systemic hypotension. One study addressed this issue by measuring pulmonary and systemic hemodynamics during pulmonary angiography. Bolus injections of nonionic contrast media, when coupled with oxygen inhalation, did not cause any major adverse hemodynamic effects, even in the presence of severe pulmonary hypertension.

Pulmonary angioscopy can play a valuable role in confirming the presence of chronic thromboembolic obstruction and in determining whether it is accessible to surgical intervention. The pulmonary angioscope is a fiberoptic device that allows visualization of the pulmonary arteries to the segmental level. The normal pulmonary artery has a round or oval contour with a smooth, pale, glistening appearance to the intima, and with bright red blood filling the lumen. The features of organized chronic emboli consist of roughening or pitting of the intimal surface, bands and webs across the lumen, pitted masses of thrombotic material within the lumen, and partial recanalization.

Currently, pulmonary angiography and angioscopy remain the cornerstone procedures for the diagnosis of CTEPH and in confirming the surgical accessibility of the obstructing lesions. Computed tomography (CT) can be useful in the evaluation of competing diagnostic possibilities such as pulmonary artery sarcoma, fibrosing mediastinitis, and extrinsic vascular compression related to malignancies or inflammatory disease. Large vessel pulmonary arteritis can also mimic certain of the angiographic findings of chronic thromboembolic disease. Arch aortography may be useful if this diagnosis is being considered.

A variety of abnormalities can be appreciated on helical CT scans obtained in patients with CTEPH, including right ventricular enlargement, chronic thromboembolic material within dilated central pulmonary arteries, bronchial artery collateral flow, and mosaic attenuation of the pulmonary parenchyma. The detection of central disease by CT scanning does not necessarily imply that the patient represents an operative candidate. A syndrome of primary pulmonary hypertension with secondary, central pulmonary artery thrombosis has been described, a situation in which surgical intervention is contraindicated. Furthermore, CT scanning lacks sensitivity in detecting chronic

thromboemboli at the segmental level as well as chronic thrombus that is well endothelialized rather than intraluminal. Both segmental-level disease and endothelialized disease are amenable to surgical intervention. Until more information is available regarding helical CT scanning in this patient population, it should be considered an adjunctive study that may provide information additive to that obtained by angiography or angioscopy.

Several other essential issues must be considered before surgery. It is important that the patient be protected against embolic recurrence, both during the high risk perioperative period and over the long term. Therefore, an inferior vena caval filter is routinely placed before surgery unless an obvious nonleg or nonpelvic source of embolism is present. To avoid the development of bleeding complications at the insertion site in the postoperative period, the filter is placed several days before surgery, preferably by a percutaneous transfemoral approach.

For those patients at risk of coronary artery disease, coronary angiography is routinely performed before surgery, usually at the time of the right ventricular catheterization and pulmonary angiography. Coronary artery bypass grafting, if necessary, can be performed at the time of the thromboendarterectomy.

The decision to proceed to pulmonary thromboendarterectomy in patients suffering from CTEPH is based on both objective and subjective factors, which are carefully defined during the preoperative evaluation.

The first and most important criterion for potential surgical intervention is the accessibility of the thrombi, as defined by angiography and angioscopy. Present surgical techniques allow removal of chronic thrombi whose proximal location extends to the main, lobar, and segmental arteries. Endarterectomy has little chance of removing lesions that begin more distally, and the procedure itself is dangerous for those with pulmonary hypertension caused by *distal disease*. Failure to remove sufficient embolic material to lower pulmonary vascular resistance, especially in patients with severe pulmonary hypertension and right ventricular dysfunction, can result in (1) an inability to wean patients from cardiopulmonary bypass at the time of thromboendarterectomy and (2) negative long-term outcomes in those who survive the procedure.

The second criterion involves the presence of hemodynamic or ventilatory impairment as a consequence of the chronic thromboembolic pulmonary vascular obstruction. Most surgical candidates have a pulmonary vascular resistance in excess of 300 dynes sec/cm^{-5}, at rest or with exercise. Occasional patients, especially those with involvement of one main pulmonary artery, have a significant exercise impairment caused by high minute ventilatory demands, without substantially altered pulmonary hemodynamics.

The option of surgery is also considered in those patients with only moderate degrees of pulmonary hypertension at rest but who develop striking levels of pulmonary hypertension with minimal exercise. Because this hemodynamic response reproduces events during the patient's activities of daily living, it may reflect the true workload of the right ventricle. Furthermore, given what is now suspected about the pathophysiologic mechanisms of the disease, it is possible that the exercise-related augmentation of pressure and flow over a sufficient period of time will result in progressive levels of pulmonary hypertension.

The third criterion involves the presence and severity of comorbid conditions (e.g., severe parenchymal lung disease), which can adversely affect outcome. Although the presence of other disease processes does not represent an absolute contraindication to the procedure, the risks imposed by any coexistent condition and its potential effect on long-term outcome are carefully reviewed with the patient before a surgical decision is made. Age by itself is not a contraindication to the procedure. Patients up to 82 years of age, if they are otherwise fit, have successfully undergone a pulmonary thromboendarterectomy.

Finally, the patient must be willing to accept the morbid and mortal risks of the corrective procedure. Patient and family cooperation and motivation are very important in the postoperative period.

Although a thoracotomy approach to CTEPH has been used in the past, sternotomy with cardiopulmonary bypass and periods of circulatory arrest currently comprise the procedure of choice. The most critical need for sternotomy arises from the bilateral

nature of the disease process. Sternotomy allows access to both pulmonary arteries and assures more complete removal of the chronically obstructing material. Cardiopulmonary bypass allows periods of complete circulatory arrest, which provides the bloodless operative field essential for meticulous lobar and segmental dissections. Finally, the presence of bronchial artery collateral flow and pleural adhesions makes a transthoracic approach difficult.

It should be emphasized that thromboendarterectomy bears no resemblance to acute pulmonary embolectomy. The intimal layer overlying chronic thrombi (*neointima*) in chronic thromboembolic disease is deceptive and is often not easily recognizable. The procedure is a true endarterectomy, requiring careful dissection of chronic endothelialized material from the native intima to restore pulmonary arterial patency. Establishing the correct plane is essential and requires a considerable degree of surgical experience and expertise. Too deep a plane will result in perforation of the vessel; too superficial a plane will not result in an adequate endarterectomy.

Periods of circulatory arrest are limited to 20-minute intervals. With experience, the entire unilateral endarterectomy usually can be accomplished within this time. If additional arrest time is necessary to complete the thromboendarterectomy, reperfusion is carried out until the venous saturations reach 90%, or for a minimum of 10 minutes.

At the completion of the bilateral endarterectomy, circulation is re-established and the patient rewarmed. The atrial septum is routinely inspected, because an atrial septal defect or persistent foramen ovale is seen (and subsequently repaired) in approximately 25% of cases. If additional procedures are required (e.g., coronary bypass grafting or valve replacement), they are performed during the rewarming period.

Careful postoperative management is essential for a successful outcome following pulmonary thromboendarterectomy. Although pulmonary hemodynamics immediately improve in most patients, the postoperative course can be complex. In addition to complications common to other forms of cardiac surgery (arrhythmias, atelectasis, wound infection, pericardial effusions, delirium), patients undergoing pulmonary thromboendarterectomy often experience three unique postoperative conditions capable of significantly impairing gas exchange and hemodynamic stability: pulmonary artery *steal*, reperfusion pulmonary edema, and persistent pulmonary hypertension.

Pulmonary artery *steal* represents a postoperative redistribution of pulmonary arterial blood flow away from previously well-perfused segments and into the newly endarterectomized segments. Although the basis for this phenomenon remains speculative, it is likely related to the temporary development of differential resistances and the loss of normal vasoregulation in the pulmonary vascular bed following thromboendarterectomy. Long-term follow-up has demonstrated that pulmonary vascular steal resolves in most patients.

Reperfusion pulmonary edema appears to represent a form of high permeability lung injury (acute respiratory distress syndrome) that is limited to those areas of lung from which proximal thromboembolic obstructions have been removed. It can appear up to 72 hours after surgery and is highly variable in severity, ranging from a mild form of edema, resulting in postoperative hypoxemia, to an acute, hemorrhagic, and fatal complication. When associated with pulmonary artery steal, reperfusion pulmonary edema can represent a significant challenge in terms of postoperative gas exchange because pulmonary blood flow is directed toward edematous, noncompliant areas of lung, which contribute poorly to gas exchange.

Management of reperfusion edema, as with other forms of acute lung injury, is supportive until resolution occurs. The judicious use of inverse ratio ventilation has proved useful in improving ventilation/perfusion relationships and gas exchange when conventional ventilatory support has failed. Nitric oxide, delivered at a concentration of 20 ppm, has also proved beneficial in improving gas exchange, although its effect on mortality remains unclear. Finally, extracorporeal oxygen support has been used successfully when conventional measures have failed.

Patients posing the most difficult management problem in the postoperative period are those with persistent pulmonary hypertension following thromboendarterectomy. This outcome is the result of either distal, surgically inaccessible thromboembolic disease or to a secondary, small vessel arteriopathy and is associated with a poor short-term and long-term outcome. Unless right ventricular afterload is substantially reduced

at the time of surgery, even patients with well-compensated right ventricular function before the procedure can experience postoperative hemodynamic instability and a low output state as a result of the depressant effects of cardiopulmonary bypass, deep hypothermia, acidosis, and hypoxemia.

The initial step in the management of these patients should occur in the operating room. In patients with severe pulmonary hypertension in whom an inadequate thromboendarterectomy is achieved, a patent foramen ovale, if present, is not closed as is routinely performed in patients undergoing this procedure. In patients in whom difficulty is encountered on attempted discontinuation of cardiopulmonary bypass because of right ventricular failure, enlargement of an existing patent foramen ovale or creation of an atrial sepal communication may prove valuable. The potential benefits of such an intervention include a decrease in right atrial pressure, an increase in cardiac output and systemic oxygen transport, and improved right coronary artery perfusion. Of course, such an intervention is an irrevocable one associated with severe postoperative hypoxemia and should only be attempted when weaning from cardiopulmonary bypass cannot be achieved in the setting of maximal pharmacologic support and when other potentially reversible conditions (hypothermia, electrolyte imbalance) responsible for the right ventricular dysfunction have been addressed.

The early intensive care management goals for the patient with persistent pulmonary hypertension and right ventricular failure following attempted thromboendarterectomy should be directed toward minimizing systemic oxygen consumption, maximizing right ventricular preload, and providing aggressive inotropic support. The use of afterload reduction in this patient population is fraught with difficulty. Pulmonary vascular resistance is commonly fixed and attempts at pharmacologic manipulation of right ventricular afterload (sodium nitroprusside, calcium channel blockers) may simply decrease systemic blood pressure and right coronary artery perfusion pressure. Inhaled nitric oxide at a concentration of 20 to 40 ppm is theoretically ideal for this circumstance because it has negligible systemic effects. Experience with this intervention in the setting of persistent postoperative pulmonary hypertension, however, has been disappointing.

At the University of California San Diego Medical Center, the operative and perioperative mortality rate in the 196 patients who underwent pulmonary thromboendarterectomy before 1990 was 15.8%. During development and early experience with this procedure, mortality was related to many causes. In the 985 patients operated between 1990 and 1999, 71 patients died, giving an in-hospital mortality rate of 7.2%. During this latter timeframe, the major causes of death were related to reperfusion pulmonary edema and to residual postoperative pulmonary hypertension and right ventricular failure when pulmonary thromboendarterectomy failed to achieve substantial improvement in pulmonary hemodynamics. Other centers involved with this procedure have experienced the same learning curve. The need for a coordinated, multidisciplinary team to manage the care of these patients cannot be emphasized too strongly. Experience and expertise in the evaluative, surgical, and postoperative aspects of care are essential to minimize the substantial morbidity and mortality associated with the surgical correction of this disease state.

Among survivors of thromboendarterectomy, the immediate hemodynamic improvement observed has been dramatic, with marked reductions in pulmonary artery pressures and pulmonary vascular resistance. Echocardiography demonstrates a decrease in right atrial and right ventricular chamber size, normalization of the interventricular septum, and improvement or resolution of tricuspid regurgitation. This improvement is reflected in the patient's postoperative physical examination and symptomatic status.

The long-term hemodynamic and symptomatic outcomes have been equally dramatic. Symptomatic improvement continues for periods as long as 9 to 12 months following surgery. This long-term improvement probably involves resolution of the patients' postoperative anemia and deconditioned state as well as an improvement in their ventilation/perfusion balance as the postoperative pulmonary artery steal resolves. In addition, resolution of the pulmonary hypertensive changes within the pulmonary vascular bed, suggested by preliminary scan and angiographic data, further reduces right ventricular afterload. Most patients, who were initially in New York Heart Association (NYHA) class III or IV status preoperatively, return to NYHA

class I or II status and are able to resume normal activities. One follow-up of 308 patients surveyed a mean of 3.3 years after surgery found that 62% of patients who were unemployed before thrombo-endarterectomy had returned to work.

In approximately 5% to 10% of cases, pulmonary thromboendarterectomy does not entirely resolve the obstruction to pulmonary arterial blood flow. This phenomenon is observed in patients whose disease involves a substantial component of distal, surgically inaccessible thromboemboli, as well as in those who have developed severe, irreversible secondary pulmonary hypertensive changes in their distal pulmonary vascular bed. In certain carefully selected patients with a significant component of surgically inaccessible disease, thromboendarterectomy can improve pulmonary hemodynamics and functional status and prolong life. Lung transplantation remains a viable option for those patients in whom severe pulmonary hypertension ultimately recurs.

All patients are maintained on lifelong anticoagulation with warfarin. No thromboembolic recurrence has been experienced by any patient maintained on therapeutic levels of anticoagulation, although it has recurred in several patients in whom anticoagulation was discontinued or was allowed to fall to a subtherapeutic level. Also, I have seen no instance of occlusion of the inferior vena caval filter.

In summary, experience over the past 20 years has demonstrated that chronic thromboembolic pulmonary hypertension represents a potentially treatable form of pulmonary hypertension, and that pulmonary thromboendarterectomy, when performed at a center experienced in the management of these patients, can restore severely compromised patients to a near-normal or normal hemodynamic and symptomatic status.

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67. UNUSUAL FORMS OF EMBOLISM

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Because the lung receives all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a *sieve* for all particulate substances entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result, the pulmonary vascular bed can be exposed to a wide variety of potentially obstructing and injurious agents. (Pulmonary thromboembolism is considered in chapters 60–62.) This chapter will discuss common forms of nonthrombotic emboli.

Among infectious agents that embolize to the lungs, schistosomiasis is the most common on a worldwide basis, although not within the United States. Schistosomiasis is caused by one of a variety of blood flukes: *Schistosoma haemotobium* (Africa and Middle East), *Schistosoma japonicum* (Japan, China, Philippines), *Schistosoma mansoni* (Africa, Arabia, South America), *Schistosoma Mekong* (Laos, Thailand), and *Schistosoma intercalatum* (Africa) are among the most common. Limited data suggest that cardiopulmonary schistosomiasis is seen most often in *S. mansoni* and *S. Japonicum* infection.

Infection occurs after contact with water containing the infective stage of the parasite, the cercaria. The cercaria penetrate unbroken skin and subcutaneous tissue and migrate through the lungs and then to the portal vein, probably by an intravascular route. The maturing schistosomes pair in the portal vein and then migrate to the venules of the mesentery, bladder, or ureters and begin to deposit eggs, many of which are subsequently swept back to the liver. During acute infection (Katayama fever), nonspecific influenzalike symptoms, abdominal pain, lymphadenopathy, hepatosplenomegaly, and blood eosinophilia associated with fleeting chest radiographic abnormalities can occur.

Pulmonary hypertension develops in fewer than 5% of infected patients; although, in endemic areas, schistosomal disease is the most common cause of cor pulmonale. The liver is involved, usually extensively, before pulmonary involvement occurs. In fact, cor pulmonale related to schistosomal infection usually does not occur in the absence of concomitant schistosomal liver disease. Pulmonary vascular obstruction appears to be induced by two mechanisms: (1) anatomic obstruction by the organism itself and (2) an intense, granulomatous, inflammatory vasculitic response to shunted and embolized schistosomal eggs.

The premortem diagnosis of cardiopulmonary schistosomiasis depends on the detection of viable schistosomal ova in stool, urine, or tissue (rectal mucosa or lung) along with evidence of hepatic fibrosis and pulmonary hypertension. Currently used serologic tests only indicate past or present infection, although promising serologic markers capable of differentiating acute from chronic disease are being investigated. Treatment with praziquantel can effectively eradicate schistosomal infections in the acute phase of the disease with minimal toxicity. However, chronic cardiopulmonary manifestations are not likely to be reversible given the fibrotic changes that are present.

An increasingly common form of nonthrombotic embolism in the United States is venous air embolism. The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma. The simple, inadvertent transection or loss of closure of a large-bore intravenous catheter, particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, can enter the arterial system and be distributed diffusely throughout the body by way of either an intracardiac shunt (atrial septal defect, patent foramen ovale) or, more likely, through microvascular pulmonary shunts.

Physiologic consequences include an abrupt rise in pulmonary artery pressure. Noncardiogenic pulmonary edema can develop, lung compliance falls, and hypoxemia ensues. The symptoms of venous air embolism, which are variable and nonspecific, can include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom. These and other consequences appear to be caused by two phenomena: (1) actual lodging of the bubbles in capillary beds, which interferes with nutrient supply to the affected organs, and (2) the formation of platelet-fibrin aggregates, creating diffuse microthrombi. Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, the severity of which depends on the rate and volume of air gaining access to the systemic arterial circulation.

Prevention and early detection are really the best approach to air embolism. Treatment focuses on restoring blood flow and promoting reabsorption of the intravascular air. Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and the early institution of hyperbaric oxygen therapy. Recovery following delayed institution of hyperbaric oxygen has been reported. Mortality from venous air embolism has been dramatically reduced through the use of such aggressive measures.

Another reasonably frequent and dramatic form of nonthrombotic embolism is fat embolism. Following entry of neutral fat into the vascular system, a rather characteristic syndrome occurs, which consists of the onset of dyspnea, hypoxemia, petechiae, and mental confusion. Seizures and focal neurologic deficits have been described. A variable lag time of 24 to 72 hours is seen in the onset of the syndrome following the inciting event; rarely, cases occur within 12 hours or as late as 2 weeks after the event. By far, the most common inciting event is traumatic fracture of long bones, with the incidence of the syndrome rising with the number of long-bone fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally cause the same syndrome. Fat embolism syndrome also has been reported following both liposuction and lipoinjection procedures, although much less frequently.

The variability in incidence of the syndrome after apparently comparable injuries has not been well defined; neither has the reason for the delay in clinical presentation been explained. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat. The latter effect is probably the more important one, causing diffuse vasculitis and leakage from cerebral, pulmonary, and other vascular beds. The time necessary to produce toxic intermediaries may explain the delay from the inciting event to clinical presentation.

The diagnosis of fat embolism syndrome is made on clinical grounds and is suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the

proper clinical context. Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20% to 50% of cases. Their absence, therefore, should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome. Fat can be demonstrated in the serum of most fracture patients with evidence of fat embolism syndrome. The finding of lipid-laden cells in bronchoalveolar lavage fluid appears to occur commonly in patients with traumatic injuries, irrespective of the presence of fat embolism syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. The role of corticosteroid therapy to prevent the onset of fat embolism syndrome after an inciting event remains controversial. Supportive treatment, including mechanical ventilation when necessary, is the primary approach, and survival is now the rule with meticulous support.

Another special form of embolism is amniotic fluid embolism, a rare, but unpredictable and catastrophic complication of pregnancy that represents the third leading cause of maternal mortality. This disorder occurs during or after delivery when amniotic fluid gains access to uterine venous channels and, therefore, to the pulmonary and general circulations. It can occur with either spontaneous delivery or with cesarean section; the delivery itself is usually uneventful. Most cases occur during labor, but delayed onset of symptoms up to 48 hours after delivery can occur. Advanced maternal age, multiparity, premature placental separation, fetal death, and meconium staining of amniotic fluid have been associated with increased risk of amniotic fluid embolism.

Amniotic fluid embolism syndrome is primarily a clinical diagnosis. An unexpected, sudden onset of severe respiratory distress, cyanosis, hypotension, cardiovascular collapse, and, often, disseminated intravascular coagulation occurs. Occasionally, seizures occur. It has been postulated that a biphasic pattern of hemodynamic disturbance exists in these cases: an initial period of pulmonary hypertension, commonly seen in animal models, followed by left ventricular dysfunction and cardiogenic shock. Patients who survive the first several hours can develop noncardiogenic pulmonary edema coincident with improvement in left ventricular dysfunction.

Amniotic fluid does contain particulate materials that can cause pulmonary vascular obstruction, but the major pathogenetic mechanism of the syndrome remains uncertain. Amniotic fluid does have thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, in other organs. As a consequence of fibrin deposition, a severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. Following the acute event, an enhanced fibrinolytic state often occurs.

The diagnosis of amniotic fluid embolism is based on a compatible clinical picture, often enhanced by finding amniotic fluid components in the pulmonary circulation. The presence of squamous cells in pulmonary arterial blood, once considered pathognomonic, has proved to be a nonspecific finding. Serological assays and immunohistochemical staining techniques have been described as having high sensitivity for amniotic fluid embolism. Validation will be required before being introduced into clinical practice.

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate), the best approach is supportive. Pulmonary artery catheterization is essential to monitor left ventricular function and volume status and to guide the appropriate utilization of inotropic and vasoactive agents. Even in the setting of aggressive supportive measures, however, maternal mortality has approached 80%.

Septic embolism is another special disorder that, unfortunately, is also increasing in frequency owing to widespread intravenous drug abuse and the expanding use of indwelling intravenous catheters. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis caused by both septic abortion and postpuerperal uterine infection. However, almost any venous structure can be involved, either as a focus of primary infection or from intravascular or contiguous spread. Examples include septic cavernous sinus thrombosis resulting from meningitis, sinusitis, or facial cellulitis; septic portal vein thrombosis resulting from diverticulitis or liver abscess; and septic tonsillar or internal jugular vein thrombosis (Lemierre's syndrome) resulting from oropharyngeal infection. Increasingly common causes are those related to intravenous drug use and those that are iatrogenic, namely, infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.

Microscopically, septic phlebitis consists of purulent material admixed with fibrin-rich thrombi. Embolization obstructs small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, the chest roentgenogram displays scattered pulmonary infiltrates that undergo cavitation. An increasing number of such infiltrates develop over periods of hours to a few days. Symptoms and signs include a high fever, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is the source of the infection, it should be removed. If a prompt response does not occur to this regimen, surgical isolation or resection of the septic vein should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis can complicate septic phlebitis, or mimic it, particularly in drug addicts.

Involvement of the pulmonary vascular bed by tumor cells is relatively common, as demonstrated by the frequency with which circulating tumor cells can be identified in patients with a wide range of malignancies and the frequency with which tumor emboli are discovered as an incidental finding at autopsy. Tumor embolism becomes clinically apparent, however, in only a few patients with malignancy.

Microvascular tumor embolism is associated with a wide range of malignancies, the most common sites of origin being the breast, lung, prostate, stomach, and liver. Tumor embolism of large fragments, which occurs rarely, can mimic acute thromboembolic disease. In this setting, survival following tumor embolectomy has been reported.

The clinical presentation of microvascular tumor embolism is typically subacute and involves progressive dyspnea, tachycardia, and tachypnea. Jugular venous distention, a prominent P_2, tricuspid regurgitation, or a right-sided S_3 may be present on physical examination if the extent of pulmonary vascular obstruction is sufficient to cause pulmonary hypertension.

The development of pulmonary hypertension is a common accompaniment of symptomatic, microvascular tumor embolism and remains a major cause of mortality. Pulmonary hypertension appears to result from both an obliteration of the pulmonary vascular bed by an admixture of tumor cells and thrombus as well as the development of medial hypertrophy, intimal fibrosis, and fibrinoid necrosis encountered in other variants of pulmonary hypertension.

Hypoxemia and a compensated respiratory alkalosis are commonly present. Most often, the chest radiograph is normal but focal or diffuse infiltrates, which may be fleeting, have been described. Ventilation-perfusion scanning most commonly demonstrates a mottled appearance or peripheral, subsegmental defects. Segmental or larger defects, indistinguishable from those associated with thromboembolic embolism, can occur in those rare instances of large-vessel obstruction. Computed tomography may demonstrate peripheral, wedge-shaped defects consistent with infarcts; a pattern of multifocal dilatation and beading of the peripheral pulmonary arteries has been described. In the setting of pulmonary hypertension, echocardiographic findings will reflect that diagnosis and include evidence of right atrial and right ventricular hypertrophy, abnormal septal position and motion, and a tricuspid regurgitant envelope consistent with elevated pulmonary artery pressures.

Pulmonary angiographic findings, most commonly, are normal. However, delayed vascular filling, pruning, and tortuosity, similar to that seen in other forms of small-vessel pulmonary hypertension, may be encountered. The angiographic findings in large, fragment tumor embolism can resemble those seen in acute thromboembolic disease.

Pulmonary microvascular cytology on specimens aspirated through a wedged pulmonary artery catheter may demonstrate malignant cells. Positive cytologies, however, can also be obtained in the setting of lymphangitic carcinomatosis. It should also be emphasized that the misidentification of megakaryocytes obtained in this manner has been reported to lead to false-positive findings.

Although diagnosis by transbronchial biopsy has been reported, diagnostic confirmation may require open-lung biopsy. Before proceeding to that step, however, it must be stressed that the impact of early diagnosis on outcome is uncertain. This intervention should only be considered in the setting of a primary malignancy for which effective chemotherapeutic options are available.

The differential diagnosis of tumor embolism includes thrombotic embolism, parenchymal metastasis, lymphangitic carcinomatosis, malignant pericardial effusion,

and chemotherapy-related lung toxicity. The premortem diagnosis is often one of exclusion. Parenchymal metastasis, lymphangitic carcinomatosis, and chemotherapy-related lung toxicity can be differentiated from tumor embolism by findings on high-resolution computed tomography. Differentiation of tumor embolism from thrombotic embolism can be somewhat more problematic, especially in cases of large vessel involvement. Under most circumstances, however, pulmonary angiography can differentiate thrombotic embolism from microvascular tumor embolism.

Because of its sieve function, the lung can also occasionally be embolized by a wide variety of other materials. Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during pregnancy. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and of bone marrow after cardiopulmonary resuscitation.

Finally, in this era of intravenous drug abuse, noninfectious vasculitic-thrombotic complications are being seen with increasing frequency in association with the intravenous use of drugs intended for oral use. Medications implicated in this syndrome include methylphenidate hydrochloride, oral opiates (pentazocine, meperidine), and antihistamines. Particulate and irritant drug carriers (e.g., talc, cellulose) and, occasionally, the drugs themselves can cause vascular inflammation and secondary thrombosis. The clinical presentation can be diverse and includes lower lobe emphysema, diffuse interstitial fibrosis, and progressive massive fibrosis. Repetitive insults can lead to severe and irreversible pulmonary hypertension. In many intravenous drug users, perfusion scans demonstrate segmental or smaller defects. Distinguishing these defects from those caused by venous thromboembolism can be difficult.

The diagnosis is often suggested by the clinical history. Radiographic findings include small, diffuse, well-defined nodular densities. These nodules can progress and massive fibrosis can ensue. Lower lobe emphysematous changes may also be present. Diagnostic confirmation often requires lung biopsy, either open or transbronchial. The prognosis is poor, and progressive pulmonary disease is common.

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68. PULMONARY HYPERTENSION: PATHOGENESIS AND ETIOLOGY

Richard N. Channick and Lewis J. Rubin

Pulmonary hypertension encompasses several distinct disease processes affecting the cardiopulmonary system. Understanding the physiology of the normal pulmonary vasculature and the pathophysiologic derangements that can arise is essential in formulating an organized approach to the diagnosis and management of these varied disorders.

Under normal conditions, the pulmonary arterial bed is a high-flow, low-pressure, low-resistance circuit. This condition allows the relatively thin-walled right ventricle to maintain adequate cardiac output, even in the face of high demand. With situations leading to increased cardiac output, for example, during exercise, pulmonary capillaries are capable of distending to accommodate the increased flow, and previously closed capillary beds are recruited. As a result, pulmonary vascular resistance decreases and pulmonary arterial pressure rises only minimally despite large increases in flow.

The common finding in all pulmonary hypertensive states is a reduction in the cross-sectional area of the pulmonary vascular tree. Initially, this derangement may be manifested solely by a loss of recruitability and dispensability of small *resistance vessels*. Pulmonary arterial pressures and vascular resistance, thus, can remain normal under resting conditions. With increases in flow, however, pulmonary arterial pressure increases.

As the pulmonary hypertensive process progresses and the cross-sectional area is further compromised, *resting* pulmonary hypertension will ensue. Pulmonary artery resistance increases and the right ventricle must generate higher pressures to maintain flow. To sustain these increased pulmonary arterial pressures, the right ventricle must transform into a more muscular chamber. In practical terms, markedly elevated pulmonary arterial pressures always indicate a chronic process in which the right ventricle has had an opportunity to hypertrophy.

In all forms of pulmonary hypertension, the clinical manifestations depend on the degree to which the right ventricular can compensate for the high afterload. With mild pulmonary hypertension, cardiac output is appropriately augmented in response to increased demand (e.g., exercise); symptoms, thus, may be minimal. In more severe pulmonary hypertension, however, the right ventricle is unable to achieve an appropriate rise in cardiac output. These patients, typically, will have exertional symptoms (dyspnea, fatigue), but no manifestations of right-sided heart failure. Eventually, if the right ventricular afterload is great enough, right-sided heart failure will ensue, manifested by resting dyspnea, jugular venous distention, hepatic congestion, ascites, and dependent edema.

A reduction in the pulmonary vascular cross-sectional area can result from three pathologic processes: vasoconstriction, obstruction, or obliteration. In most forms of pulmonary hypertension, more than one of these processes are present. For example, pulmonary vasoconstriction, which can be present in primary pulmonary hypertension, chronic hypoxia, cardiac disease, and parenchymal lung disease, leads to hypertrophy of the pulmonary arterial medial layer. This structural change results in further compromise of the vessel's lumen. As a result, vascular wall tension increases, leading to proliferation and scarring in the intima and further obliteration of the peripheral vessels and *fixed* pulmonary hypertension. In fact, these small-vessel structural lesions, including muscular hypertrophy, intimal proliferation, and fibrosis, are common end points in virtually all forms of long-standing pulmonary hypertension.

The factors leading to vasoconstriction and the various histopathologic lesions described are complex. A delicate balance exists between mediators that maintain the pulmonary vascular bed in a relatively dilated, nonproliferating, nonthrombotic state (prostacyclin, nitric oxide, tissue plasminogen activator, and heparinlike growth inhibitors) and those that promote constriction, proliferation, and thrombosis (thromboxane A_2, platelet-activating factor, endothelin-1, plasminogen-activator inhibitor, and growth factors). Perturbations in this balance lead to the development of hypertensive changes in the pulmonary vasculature. Additionally, abnormalities in outward

potassium current (KV) have been described in patients with primary pulmonary hypertension. Interestingly, a similar effect on K+ channels is seen in vitro with exposure of pulmonary artery smooth muscle cells to dexfenfluramine, a *diet pill* associated with primary pulmonary hypertension. Despite advances in knowledge of molecular and cellular mechanisms, a cohesive pathogenic scheme for pulmonary hypertension remains to be elucidated.

Pulmonary hypertension can be caused by one of four fundamental mechanisms: (1) primary cardiac diseases; (2) pulmonary parenchymal diseases; (3) hypoventilatory syndromes; and (4) primary pulmonary vascular diseases.

Primary cardiac diseases lead to pulmonary arterial hypertension through two primary mechanisms: impairment of pulmonary venous outflow and increased pulmonary blood flow. For example, left ventricular dysfunction and mitral stenosis both lead to elevated pulmonary venous pressure. This results in mild pulmonary arterial hypertension, augmented to some degree by vasoconstriction. Over time, microvascular changes (e.g., muscular hypertrophy and intimal proliferation) can occur, leading to sustained pulmonary arterial hypertension, even after pulmonary venous pressure is reduced (e.g., by repair of the mitral stenosis).

Atrial and ventricular septal defects lead to pulmonary hypertension through remodeling of the pulmonary vasculature as a result of chronic high intrapulmonary flow. The resulting microvascular changes are similar to those noted in other forms of pulmonary hypertension. A hallmark of septal defect-associated pulmonary hypertension is augmented right-to-left intracardiac shunting (Eisenmenger's physiology), resulting in significant arterial hypoxemia. Under these circumstances, closure of the septal defect can worsen pulmonary hemodynamics and induce overt right ventricular failure.

Pulmonary parenchymal diseases, including chronic obstructive pulmonary disease (COPD), interstitial lung disease, and widespread parenchymal destructive processes (tuberculosis), can lead to significant pulmonary hypertension. Both obliteration of the pulmonary vascular bed and hypoxic vasoconstriction can contribute to the pulmonary hypertensive state.

In COPD, the degree of pulmonary hypertension generally reflects the severity of gas exchange impairment rather than the extent of parenchymal destruction. Pulmonary hypertension in this group is generally modest (i.e., mean pulmonary arterial pressures are typically less than 40 mm Hg). Pulmonary hypertension out of proportion to the degree of gas exchange derangement or a rapid worsening of previously mild pulmonary hypertension in a patient with COPD should raise suspicion for a superimposed process, such as thromboembolism or sleep apnea.

Interstitial lung disease can lead to severe pulmonary hypertension through both vasoconstriction and obliteration of small pulmonary arteries. Typically, however, severe restriction is necessary before pulmonary hypertension develops (i.e., lung volume reduction of ≥50%). The same is true of destructive lung disorders. Therefore, severe pulmonary hypertension should not be attributed to mild restrictive lung disease. In fact, in both *primary* and thromboembolic pulmonary hypertension, a mild pulmonary restrictive defect (mean forced vital capacity and total lung capacity of approximately 80% of predicted) is often encountered.

Hypoventilation syndromes, including sleep apnea, central alveolar hypoventilation, and obesity-hypoventilation syndrome, can be associated with generally mild pulmonary hypertension induced by hypoxemia, hypercapnia, or acidosis. The degree of pulmonary hypertension in these disorders appears to correlate with the magnitude of the gas exchange abnormalities, most notably the presence of daytime hypoxemia. Although structural vascular changes can occur with chronic hypoventilation, they are mainly limited to muscular hypertrophy and, typically, reverse after resolution of the ventilatory derangement.

Primary pulmonary hypertension (PPH) is an idiopathic disorder characterized by lesions in the small pulmonary arteries in the absence of another underlying cardiac or pulmonary disease. Histologically, a spectrum of microvascular lesions can exist in the small, resistance arteries: medial hypertrophy, intimal fibrosis, plexiform lesions (multichanneled outpouchings from arterioles and small arteries), and microthrombotic lesions. Some have suggested that PPH be divided into two distinct histopathologic types: plexogenic pulmonary arteriopathy and thrombotic arteriopathy. It is now clear that patients with PPH and, in fact, patients with most forms of pulmonary hypertension often have all of these lesions simultaneously. For example, in the

National Institutes of Health (NIH) registry of PPH patients, more than one third of patients with plexiform lesions also had microthrombotic lesions.

Primary pulmonary hypertension is an uncommon disease; its incidence is estimated at 1 to 2 per million. The disease most commonly presents during the third or fourth decade of life. A preponderance in women (1.7:1.0) has been consistently observed. The cause of PPH is unknown, although association with certain anorexic agents (aminorex, fenfluramine, dexfenfluramine), collagen vascular diseases, portal hypertension, and infection with the human immunodeficiency virus (HIV) are well recognized. Approximately 7% of cases are familial; a specific chromosomal defect (2q31–q32) has been found in some familial cases of PPH. The mode of hereditary transmission appears to be autosomal dominant with variable penetrance.

No clinical features are unique to PPH; historical data and physical examination findings merely confirm the presence of pulmonary hypertension, right-sided heart failure, or both. As with all forms of pulmonary hypertension, the diagnosis depends on a high index of suspicion as well as a logical diagnostic approach (Chapter 69).

A disorder that mimics PPH in many respects is pulmonary veno-occlusive disease. This disorder, also idiopathic, is caused by widespread occlusion of the small pulmonary veins.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct entity, characterized by obstruction of large, elastic (main, lobar, and segmental) pulmonary arteries by chronic, unresolved, organized pulmonary emboli. Pulmonary hypertension results from these obstructions and, in some patients, secondary changes that develop in the small *resistance* arteries. This entity is discussed in detail in Chapter 66.

The diagnostic workup, outlined in Chapter 66, will distinguish between CTEPH and PPH with a high level of certainty. This distinction is critical because CTEPH is potentially curable with surgical intervention, namely pulmonary thromboendarterectomy.

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1. Abenhaim L, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;335:609.
   A landmark publication describing the first case-control study that clearly demonstrated an association between PPH and prior anorexigen drug use. The association strengthened with longer use (≥3 months) and with use within the preceding year.
2. Brammell HL, et al. The Eisenmenger syndrome: a clinical physiological reappraisal. *Am J Cardiol* 1971;28:679.
   Good clinical and physiologic discussion of Eisenmenger's syndrome.
3. Christman BW, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;327:70.
   Stable urinary metabolites of thromboxane and prostacyclin were measured in normals, patients with PPH, and patients with secondary pulmonary hypertension. An increase in the ratio of thromboxane to prostacyclin was found in the PPH group, suggesting a role for this imbalance (favoring vasoconstriction and smooth muscle cell proliferation) in either the development or maintenance of PPH.
4. Dinh Xuan AT, Higenbottam TW, Clelland CA. Impairment of endothelium-dependent pulmonary artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991;324:1539.
   Lungs taken from patients with COPD undergoing transplantation were found to have diminished vascular relaxation in response to stimulation of endothelium-derived relaxing factor (by acetylcholine), suggesting a defect in either nitric oxide synthesis or effect in these vessels.
5. Gomez-Sanchez MA, et al. Clinical and pathologic manifestations of pulmonary vascular disease in the toxic oil syndrome. *J Am Coll Cardiol* 1991;18:1539.
   Describes the clear association between small-vessel pulmonary hypertension and toxic-oil inhalation.
6. Gurtner HP. Aminorex and pulmonary hypertension. *Cor et Vasa* 1985;27:160.
   An outbreak of primary pulmonary hypertension occurred in Europe between 1967 and 1973, which was traced to ingestion of the anorectic agent aminorex.

7. Hadengue A, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991;100:520.
Small-vessel pulmonary hypertension was found on right-sided heart catheterization in 2% of patients with portal hypertension, significantly higher than estimates for the general population. The cause of this association is not known, although a vasoconstrictive mediator bypassing the liver and affecting the pulmonary vasculature has been suggested.
8. Kuo PC, et al. Distinctive clinical features of portopulmonary hypertension. *Chest* 1997;112:980.
Thirty patients with portopulmonary hypertension were compared with 30 patients with PPH and 30 patients with liver disease alone. Portopulmonary hypertension is characterized by higher cardiac indices than found in patients with PPH. Respiratory alkalosis was magnified compared with patients with liver disease alone or with PPH.
9. Loyd JE, Primm RK, Newman JH. Familial primary pulmonary hypertension: clinical patterns. *American Review of Respiratory Diseases* 1984;129:194.
In the NIH Registry, 7% of cases were familial. The genetic mode of transmission is not clear; an autosomal dominant mode with variable penetrance has been noted. A spectrum of histopathologic lesions can be seen in members of the same family. No differences in presentation, hemodynamics, or natural history are noted between familial and nonfamilial cases.
10. Mesa RA, et al. Human immunodeficiency virus infection and pulmonary hypertension: two new cases and a review of 86 reported cases. *Mayo Clin Proc* 1998;73:37.
A nice review of the increasingly recognized association between HIV infection and PPH. The cause of this association is still not known. It appears that PPH associated with HIV has a more aggressive course.
11. Michelakis ED, et al. Dexfenfluramine elevates systemic blood pressure by inhibiting potassium currents in vascular smooth muscle cells. *J Pharmacol Exp Ther* 1999;291:1143.
Direct evidence for an effect of the anorexigen dexfenfluramine on potassium currents; a similar abnormality in outward K+ currents has been found in patients with PPH.
12. Morse JH, et al. Familial primary pulmonary hypertension locus mapped to chromosome 2q31–q32. *Chest* 1998;114:57S.
In cases of familial PPH (~ 5% of all cases), a chromosomal abnormality has been identified. Similar genetic abnormalities have not been found in the remainder (nonfamilial) cases.
13. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest* 1993;103:685.
Histopathologic lesions including plexiform lesions, recanalized microthrombi, medial hypertrophy, and intimal proliferation were found in patients with chronic thromboembolic pulmonary hypertension. This study refutes the commonly held belief that plexiform lesions are specific to PPH.
14. Okada K, et al. Angiotensin-converting enzyme inhibition delays pulmonary vascular neointimal formation. *Am J Respir Crit Care Med* 1998;158:939.
In an animal model, thickening of the inner layer of the pulmonary arteries was inhibited with angiotensin-converting enzyme (ACE) inhibition. Whether ACE inhibition has a role in human pulmonary hypertension, however, is not known.
15. Pietra GG, et al. Histopathology of primary pulmonary hypertension: a qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute primary pulmonary hypertension registry. *Circulation* 1989;80:1198.
A landmark study describing the histologic lesions seen in PPH.
16. Proceedings of the Brenot Memorial Symposium on the Pathogenesis of primary Pulmonary Hypertension, Corisca, July 29–31, 1997. *Chest* 1998;114:183S.
Excellent review summary of a PPH symposium.
17. Rich S, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987;107:216.
An important study that summarizes the results of the NIH PPH registry, which collected 194 cases from 32 centers between 1981 and 1985.

18. Rubin LJ. Cellular and molecular mechanisms responsible for the pathogenesis of primary pulmonary hypertension. *Pediatr Pulmonol* 1999;18:194.
A nice review of what is known about basic mechanisms in PPH.
19. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111.
A state-of-the-art review.
20. Sajkov D, et al. Pulmonary hypertension and hypoxemia in obstructive sleep apnea. *Am J Respir Crit Care Med* 1994;149:416.
A study of 14 patients with obstructive sleep apnea. The degree of pulmonary hypertension was mild (mean pulmonary arterial pressure 23 ± 2 mm Hg) and did not correlate with indices of lung function or the degree of apnea present. Pulmonary hypertension did correlate with the degree of daytime hypoxemia; the authors proposed that variation in the pulmonary vascular response to hypoxia and acidosis determines whether a patient with obstructive sleep apnea develops fixed pulmonary hypertension.
21. Salerni R, Rodnan GP, Leon DF. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). *Arch Intern Med* 1977;86:394.
Describes the frequency of small pulmonary arterial involvement in CREST; clinical manifestations are similar to idiopathic (primary) pulmonary hypertension.
22. Salvaterra CG, Rubin LJ. Investigation and management of pulmonary hypertension in chronic obstructive pulmonary disease. *American Review of Respiratory Diseases* 1993;148:1414.
A good review article. Pulmonary hypertension caused by COPD is typically mild (mean pulmonary arterial pressure < 40 mm Hg).
23. Smith P, et al. The ultra structure of plexogenic pulmonary arteriopathy. *J Pathol* 1990;160:111.
A histopathologic paper discussing mechanisms for the development of intimal proliferation and plexiform lesions.
24. Speich R, et al. Primary pulmonary hypertension in HIV infection. *Chest* 1991; 100:1268.
This association has been well documented in this and other studies, although the virus has not been isolated within blood vessel walls.
25. Stewart DJ, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease. *Ann Intern Med* 1991;114:464.
Elevated arterial levels of endothelin-1, a vasoconstrictive mediator, were found in patients with PPH. Whether this finding has pathogenetic significance in the development or maintenance of PPH or is merely a noncontributory marker of the disease is not known.
26. Yuan JX, et al. Dysfunctional voltage-gated K+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. *Circulation* 1998;98:1400.
Potassium current channels in pulmonary artery smooth muscle cells were found to be defective in PPH patients compared with patients with secondary pulmonary hypertension; suggesting a fundamental abnormality in PPH. Agents aimed at opening *these channels may have benefit.*

69. PULMONARY HYPERTENSION: DIAGNOSIS AND TREATMENT

Richard N. Channick and Lewis J. Rubin

The first challenge in the diagnostic evaluation of a patient with pulmonary hypertension is recognizing that pulmonary hypertension itself is present. Historical information is often nonspecific; dyspnea on exertion is present in virtually all patients with significant pulmonary hypertension and may be the only presenting symptom. Other common symptoms include cough (30%), chest pain (21%), hemoptysis (10%),

and easy fatigability (25%). These nonspecific symptoms often suggest other, more common, diagnostic considerations (chronic obstructive pulmonary disease [COPD], coronary artery disease, psychogenic dyspnea) rather than pulmonary hypertension. More *specific* historical information, such as a history of venous thromboembolism, known pulmonary parenchymal disease, or childhood heart murmurs should arouse suspicion for a specific pulmonary hypertensive disorder.

Physical findings also can be relatively subtle. *Classic* signs of pulmonary hypertension include accentuation of the pulmonic component of the second heart sound (S_2), fixed splitting of S_2, murmurs of tricuspid regurgitation pulmonic insufficiency (in some cases), and a left parasternal lift, indicative of right ventricular hypertrophy. One notable physical examination finding observed in some patients with chronic thromboembolic pulmonary hypertension (CTEPH) is the presence of pulmonary artery *flow murmurs*. These are bruits auscultated over the lung fields, heard best during breath holding at midinspiration. These sounds indicate flow through partially occluded central pulmonary arteries and are highly suggestive of chronic large-vessel pulmonary embolic disease.

Chest radiography may be unrevealing. If pulmonary hypertension is severe, enlargement of the right ventricle and pulmonary arteries is apparent. Chest radiography, however, can be useful in searching for secondary causes of pulmonary hypertension (interstitial lung disease, COPD). One notable radiographic finding is the presence of interstitial edema (Kerley B lines) in the setting of right ventricular and pulmonary artery enlargement. This constellation of x-ray findings should raise suspicion for pulmonary veno-occlusive disease.

The presence of pulmonary hypertension can generally be confirmed noninvasively by echocardiography. Two-dimensional echocardiography will demonstrate varying degrees of right atrial and right ventricular enlargement. Paradoxical movement of the interventricular septum indicates right ventricular pressure overload. Doppler echocardiography can also estimate the degree of pulmonary arterial hypertension. Specifically, the peak velocity (v) of the tricuspid valve regurgitant envelope corresponds to a pulmonary artery systolic pressure (PASP), which may be estimated using the formula:

$$PASP = 4 * v^2 + \text{right atrial pressure}$$

Despite the utility of an echocardiogram in suggesting a diagnosis of pulmonary hypertension, right ventricular catheterization is mandatory to make the diagnosis of pulmonary hypertension, determine the severity of disease, and assess vasoreactivity.

Pulmonary hypertension that occurs only during exercise is becoming an increasingly recognized entity. It appears that pulmonary arterial pressure is increased more readily with upper extremity exercise; therefore, arm exercise with a pulmonary artery catheter in place is recommended when this entity is suspected.

Once the diagnosis of pulmonary hypertension has been established, disclosing the specific cause (if one exists) depends on an orderly diagnostic approach. Secondary causes should be considered and excluded with the following studies: (1) echocardiography to exclude the presence of congenital heart disease (atrial septal defect, ventricular septal defect, patent ductus arteriosus) and acquired disorders (e.g., mitral stenosis or regurgitation or left ventricular dysfunction); (2) pulmonary function testing to determine if significant obstructive or restrictive lung disease is present, although parenchymal disease must be severe to cause pulmonary hypertension; (3) arterial blood gases to define a hypoventilation syndrome; (4) sleep studies, if clinically indicated; and (5) chest x-ray study and high-resolution computed tomography scanning if the diagnosis of interstitial lung disease-associated pulmonary hypertension is contemplated. With these noninvasive studies, multiple disorders can be excluded and the diagnosis narrowed down to diseases innate to the pulmonary vascular system itself. Blood tests to define the vascular process further include antibodies to the human immunodeficiency virus and antinuclear antibody titer to screen for collagen vascular disease.

Once *extravascular* causes have been excluded, the next step in the diagnostic evaluation is distinguishing between large-vessel pulmonary vascular processes (usually

chronic thormboembolic pulmonary hypertension [CTEPH] and primary pulmonary hypertension [PPH]). This diagnostic distinction is critical, as treatment for each disorder is quite different.

Ventilation-perfusion lung scanning is highly accurate in distinguishing large-vessel pulmonary hypertension from PPH. The presence of at least one and usually several segmental or greater-sized perfusion defects with normal ventilation strongly suggests the diagnosis of CTEPH. In contrast, the lung scan in patients with small-vessel pulmonary hypertension is either normal or *mottled* in appearance. It must be noted, however, that the lung scan can underestimate the degree of obstruction in CTEPH; this is important to recognize when considering treatment options and necessitates the next diagnostic procedure—pulmonary angiography.

Pulmonary angiography is indicated when suspicion for CTEPH exists, both to confirm the diagnosis and to determine the surgical accessibility of obstructing thrombi. Pulmonary angiography is not necessary when lung scanning clearly demonstrates small-vessel disease; however, if it is done, pulmonary angiography will demonstrate *pruning* of vessels beyond the subsegmental level, with absence of the *blush* that ordinarily occurs. With large-vessel CTEPH, on the other hand, several specific angiographic abnormalities have been described and are discussed in detail in Chapter 66.

The outcome of patients with untreated PPH is generally unfavorable. In the National Institutes of Health Registry of PPH patients, median survival from the time of recognition was 2.9 years. Less precise estimates are available for other forms of pulmonary hypertension, although, in general, prognosis depends on both the degree of pulmonary hypertension and the severity of right ventricular dysfunction. In PPH, variable right atrial pressure has correlated (inversely) most closely with survival. Patients can die either suddenly or after progressive heart failure.

Because outcome is dependent on the severity of pulmonary hypertension and the adequacy of right ventricular compensation, it is critical to determine the ability of the pulmonary vascular bed to vasodilate in response to pharmacologic agents. In fact, acute vasodilator testing with a pulmonary artery catheter in place is necessary before any chronic pharmacologic intervention is instituted. Agents that have been used for acute vasodilator testing include prosatcyclin, inhaled nitric oxide, and adenosine.

Treatment options in pulmonary hypertension depend on the cause. In secondary forms, treatment of the underlying process is indicated. Correcting hypoxemia with supplemental oxygen can have a beneficial effect, as will reversion of hypercapnia and acidosis. With right ventricular failure, diuretics are used, which relieve symptoms such as hepatic congestion and leg edema, and also may significantly improve dyspnea, for unclear reasons. Diuretics must, however, be used with caution, as excessive reductions in blood volume can adversely affect the preload-dependent right ventricle and lead to systemic hypotension. Digoxin is not beneficial in right ventricular failure secondary to pulmonary hypertension. However, digoxin should be considered in patients with supraventricular arrhythmias or in those who are taking medications with negative inotropic properties (e.g., calcium channel blockers).

Warfarin is recommended for patients with PPH. This recommendation is based on retrospective data indicating a significant survival benefit.

Vasodilators have little effect in secondary forms of pulmonary hypertension or CTEPH. However, approximately 20% of patients with PPH will manifest significant reductions (>20%) in both pulmonary arterial pressures and pulmonary vascular resistance in response to vasodilators. Numerous vasodilator medications have been studied, although oral calcium channel blockers appear to have fewer adverse systemic hemodynamic effects than other oral agents such as hydralazine or angiotensin-converting enzyme inhibitors.

It has been shown that if significant acute pulmonary vasoreactivity is present, patients will generally have favorable long-term responses to oral calcium channel antagonists. On the other hand, in the absence of an acute pulmonary vasodilator response, oral calcium channel blockers can be detrimental.

For patients with severe PPH (class III or IV) who have failed or are not candidates for oral calcium blocker therapy, continuous intravenous prostacyclin (epoprostenol, Flolan) is a potentially lifesaving option. Epoprostenol has been clearly demonstrated to improve exercise capacity, pulmonary hemodynamics, and survival. These benefi-

cial effects were noted even in the absence of favorable acute hemodynamic responses to the agent, suggesting that chronic prostacyclin has other, nonvasodilating effects (inotropy, vascular remodeling). Because of the complicated nature of prostacyclin therapy, this treatment should be initiated and monitored only in centers with substantial experience in the care of patients with pulmonary hypertension.

Several experimental medical therapies are being examined or contemplated for patients with PPH and some secondary forms of small-vessel pulmonary hypertension. Such therapies include a subcutaneous form of prostacyclin (UT-15), oral endothelin-1 blockers, oral prostacyclin analogs, and inhaled, selective, pulmonary vasodilators (prostacyclin, iloprost, nitric oxide). Whether any of these therapies will be determined to be useful either as alternatives to intravenous prostacyclin or as adjunctive therapies remains to be elucidated.

In some patients with severe PPH and right ventricle failure, creation of a small atrial septal defect may be clinically efficacious. This can be done by balloon septostomy, which allows blood, albeit deoxygenated, to reach the left ventricle, thereby improving cardiac output and, it is hoped, oxygen delivery. Of course, the *downside* is the resultant hypoxemia. The size of the defect created appears to be critical in balancing improvement in cardiac output against severe hypoxemia.

In recent years, lung and heart-lung transplantation have become more *standard* therapeutic options in the treatment of some forms of pulmonary hypertension (Eisenmenger's syndrome, PPH). Single or double lung transplantation are considered acceptable in most patients with pulmonary hypertension. Currently, heart-lung transplantation is generally reserved for patients with complex congenital heart abnormalities that cannot be corrected at the time of lung transplantation. Successful transplantation results in marked hemodynamic and functional improvement. However, beneficial long-term outcomes with lung transplantation have been somewhat tempered by the prevalence of chronic rejection (manifested by bronchiolitis obliterans) in approximately one third of patients.

Patients with CTEPH, on the other hand, are unique in that surgical intervention, namely pulmonary thromboendarterectomy, has been shown to dramatically relieve pulmonary hypertension, right ventricle failure, and symptoms. This improvement appears to continue long term. Thus, this group of patients has a potentially curable form of pulmonary hypertension. Surgical treatment of CTEPH is discussed in detail in Chapter 66.

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1. Barst RJ, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296.

   A landmark study demonstrating the efficacy of continuous prostacyclin in improving both exercise capacity and survival in PPH. It led to approval of epoprostenol for the treatment of class III and IV PPH.

2. Channick RN, et al. Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: an ambulatory delivery system and initial clinical tests. *Chest* 1996;109:1545.

   The first description of a technique for inhaled nitric oxide delivery to ambulatory, at-home patients. Long-term delivery of inhaled nitric oxide as a pulmonary vasodilator is feasible.

3. Channick RN, Yung GL. Long-term use of inhaled nitric oxide for pulmonary hypertension. *Respir Care* 1999;44:212.

   Summary of experience using chronic inhaled nitric oxide in pulmonary hypertension.

4. D'Alonzo GG, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991;115:343.

   Documents poor survival in PPH (median survival 2.9 years), which is strongly influenced by pulmonary hemodynamics such as right atrial pressure, mean pulmonary artery pressure, and cardiac index. A formula was derived for predicting survival in these patients.

5. D'Alonzo GG, et al. Comparison of progressive exercise performance of normal subjects and patients with primary pulmonary hypertension. *Chest* 1987;92:57.
Exercise limitation in patients with PPH is predominantly because of cardiac limitation with an inability to maintain oxygen delivery during exercise. The ventilatory response to exercise also appeared to be somewhat exaggerated in PPH patients.
6. Dev V, Shrivastava S. Time course of changes in pulmonary vascular resistance and the mechanism of regression of pulmonary arterial hypertension after balloon mitral valvuloplasty. *Am J Cardiol* 1991;67:439.
Following balloon valvuloplasty, an initial acute decrease occurred in pulmonary arterial pressures, corresponding to decreases in wedge pressure. A second gradual further decrease in pulmonary artery pressures occurred thereafter because of decreased pulmonary vascular resistance, presumably as a result of regression of pulmonary arteriopathic changes.
7. Domenighetti GM, Saglini VG. Short- and long-term hemodynamic effects of oral nifedipine in patients with pulmonary hypertension secondary to COPD and lung fibrosis. *Chest* 1992;102:708.
Fifteen patients with COPD and mild pulmonary hypertension (mean pulmonary arterial pressure 32 mm Hg) were given nifedipine. A mild reduction in mean pulmonary arterial pressure was noted 1 week into therapy; however, pulmonary arterial pressures returned to pretreatment levels by the eighth week of nifedipine use. The authors suggest that nifedipine does not generally help COPD-associated pulmonary hypertension.
8. Fedullo PF, Fishmann AJ, Moser KM. Pulmonary perfusion scans in primary pulmonary hypertension. *Chest* 1983;127:82.
Lung scanning is highly accurate in distinguishing PPH from large-vessel thromboembolic disease. A normal or mottled-*appearing scan is consistent with PPH.*
9. Frank H, et al. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest* 1997;112:714.
This study found benefit in survival with anticoagulation in patients with aminorex-induced PPH as well as in other cases of PPH. Supports previous retrospective data.
10. Georgeson S, et al. Effect of percutaneous balloon valvuloplasty on pulmonary hypertension in mitral stenosis. *Am Heart J* 1993;125:1374.
A study of 53 patients with mitral stenosis and secondary pulmonary hypertension undergoing balloon valvuloplasty. Although this procedure reduced pulmonary hypertension acutely, at 17 months follow-up recurrent pulmonary hypertension was present in many patients because of mitral regurgitation.
11. Higenbottam T, et al. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998;80:151.
Confirms the long-term survival benefit of prostacyclin infusions. Benefit was greatest in patients with worse cardiac function (SvO_2 < 60%, median survival 585 days versus 239 days with conventional therapy).
12. Hopkins WE, et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996;15:100.
Adult patients with Eisenmenger's syndrome, as a group, have better maintained cardiac function and improved long-term survival compared with PPH patients.
13. Jamieson SW, et al. Experience and results of 150 pulmonary thromboendarterectomy operations over a 29-month period. *J Cardiovasc Thorac Surg* 1993;106:116.
Describes the clinical entity of CTEPH. Reports the surgical technique and the beneficial effects of pulmonary thromboendarterectomy as the treatment of choice in properly selected patients.
14. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease: evaluation and management. *Chest* 1991;99:715.
A good overview of cor pulmonale.
15. Langleben D, et al. Continuous infusion of epoprostenol improves the net balance between pulmonary endothelin-1 clearance and release in primary pulmonary hypertension. *Circulation* 1999;99:3266.

Previous studies by this group demonstrated net production of endothelin-1 (ET-1) in the lungs of PPH patients (arterial:venous ET-1 ratio > 1) This study of 11 patients treated with long-term epoprostenol infusions demonstrated that 82% of patients had arterial:venous ET-1 ratios < 1 by day 88 of therapy, suggesting that chronic epoprostenol helps normalize endothelial function.

16. McLaughlin VV, et al. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;338:273.

Follow-up (recatheterization at 16.7 ± 5 months) hemodynamic data on 27 patients treated with prostacyclin. Confirmed a persistent improvement in pulmonary vascular resistance, which was generally lower than during the initial vasodilator test before initiation of chronic epoprostenol.

17. Perloff JK. Auscultatory and phonocardiographic manifestations of pulmonary hypertension. *Prog Cardiovasc Dis* 1967;9:303.

Classic findings include increased intensity of P_2 and narrowing of the A_2-P_2 inspiratory splitting proportional to pulmonary arterial pressures; eventually, wide A_2-P_2 splitting occurs with the advent of right ventricular failure.

18. Rich S, Brundage BH. High dose calcium channel blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987;76:135.

Those patients who responded favorably to high-dose calcium blockers maintained the improvement in pulmonary hemodynamics.

19. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76.

The first study to demonstrate improved survival in PPH patients who responded acutely to high-dose calcium channel blockers and were then continued on these agents. Very high doses of these agents were often necessary to achieve a favorable pulmonary hemodynamic response.

20. Rothman A, et al. Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. *Am J Cardiol* 1999;84:682.

Twelve patients with severe pulmonary hypertension were treated with graded balloon dilation to create a small atrial septal defect. Mean oxygen delivery improved following the procedure. Six patients had clinical improvement, 5 of whom subsequently underwent lung transplantation. This procedure may serve a role as a bridge to transplantation.

21. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999;99:1858.

This report of 20 patients with different congenital heart diseases and secondary pulmonary hypertension, demonstrated significant benefit of long-term epoprostenol on hemodynamics, exercise capacity, and functional class. It appears that, in general, epoprostenol, is effective in certain forms of secondary pulmonary hypertension.

22. Ryan KL, et al. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. *Chest* 1988;98:1180.

Although lung scans are highly useful in distinguishing CTEPH from PPH, the degree of angiographic obstruction is often substantially greater than suggested by lung scanning. This discrepancy is caused by the partial obstructions often seen in CTEPH; this may lead to significant hemodynamic compromise, although technetium-labeled albumin can pass through so that gray areas *rather than classic defects are seen.*

23. Saji T, et al. Short-term hemodynamic effect of a new oral PGI2 analogue, beraprost, in primary and secondary pulmonary hypertension. *Am J Cardiol* 1996;78:244.

Preliminary experience with an oral prostacyclin analogue.

24. Setaro JF, Cleman MW, Remetz MS. The right ventricle in disorders causing pulmonary venous hypertension. *Cardiol Clin* 1992;10:165.

An excellent review article describing the physiologic and clinical consequences of pulmonary venous hypertension.

25. Shapiro SM, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol* 1997;30:343.

Demonstrated clear survival benefit, compared with historical controls, of long-term epoprostenol infusions.

26. Soler M, Michel F, Perruchoud AP. Long-term oxygen therapy for cor pulmonale in patients with chronic obstructive pulmonary disease. *Respiration* 1991;58:52.
Reviews several studies evaluating the mechanisms of the survival effect of oxygen in this group. It appears that patients with COPD and mild pulmonary hypertension have improved survival with oxygen supplementation, whereas those with more severe pulmonary hypertension do not gain survival benefit.
27. Wimmer M, Schlemmer M. Long-term hemodynamic effects of nifedipine on congenital heart disease with Eisenmenger's mechanism in children. *Cardiovasc Drugs Ther* 1992;6:183.
Oral vasodilators are generally not efficacious in the management of Eisenmenger's syndrome.

70. HEART-LUNG AND LUNG TRANSPLANTATION

Gordon L. Yung

Human lung transplantation was first performed in 1963 but not widely accepted as a treatment for end-stage lung diseases until the early 1980s when cyclosporin was introduced into the postoperative immunosuppressive regimen. By March 1, 1998, 4777 single lung, 3278 double lung, and 2428 heart-lung transplantations had been reported to The Registry of the International Society for Heart and Lung Transplantation. As the medical community and public become more aware of this option, the demand for lung transplantation continues to grow. The number of surgeries performed, however, has not increased in parallel with the demand, mainly because of a lack of suitable donor organs. Only 15% to 20% of all potential donors have lungs suitable for transplant, reflecting the fragility of lungs as donor organs. A number of issues must be understood by the physician and patient if human lung transplantation is to succeed; these include the timing for referral, recipient selection, pretransplant follow-up, donor selection, and type of transplantation procedures, and post-transplant management.

Timing for Referral

Currently, lung transplantations are performed in the order patients are listed (i.e., patients listed earlier have a higher priority). The only exceptions are patients with idiopathic pulmonary fibrosis, who are *credited* with an extra 90 days of accumulated waiting time at the time of listing, because this disease can rapidly progress. The severity of lung disease currently does not change the order of transplantations. In the future, the severity of illness is likely to affect priority on the transplantation waiting list, as is the case for those awaiting heart or liver transplantations. Consequently, long waiting times (≥2 years in some programs) are common and underscore the importance of referring suitable patients as soon as it becomes apparent that lung transplantation is appropriate.

The optimal timing for recipient referral is based on the natural history of the underlying lung disease; guidelines are presented in Table 70.1. The guidelines are not rigid because various lung conditions progress at different rates and, furthermore, a patient's course can vary widely for each disease. Each patient should be considered individually. In the past, patients were only considered for transplant when the expected survival without surgery was less than 1 to 2 years despite optimal therapy. However, advances in medications, surgical techniques, and post-transplant care have improved the outcome after lung transplantation significantly. Currently, the overall survival after single lung transplants is approximately 3.6 years, and after bilateral lung transplants approximately 4.5 years. Therefore, patients should be considered

Table 70.1. Referral Guidelines for Selected Diseases

Chronic obstructive pulmonary disease
–FEV_1 < 20% to 25% predicted or ≤ 500 ml
–CO_2 retention (≥55 mm Hg)
–Pulmonary hypertension
–Severe hypoxemia (<55–60 mm Hg)
–Rapid deterioration
Cystic fibrosis
–FEV_1 < 30% predicted
–CO_2 retention (≥50 mm Hg)
–Pulmonary hypertension
–Severe hypoxemia (<55 mm Hg)
–Rapid deterioration
Idiopathic pulmonary fibrosis
–VC or TLC < 70% predicted
–DLCO < 60% predicted
–Pulmonary hypertension
–Resting hypoxemia
–Deterioration despite therapy
Primary pulmonary hypertension
–NYHA functional class III or IV
–Cardiac index < 2 L/min/m^2
–Right atrial pressure > 10–15 mm Hg
–Mean pulmonary artery pressure ≥ 50–55 mm Hg

FEV_1, forced expiratory volume in 1 second; VC, vital capacity; TLC, total lung capacity; DLCO, diffusing capacity of lung for carbon dioxide; NYHA; New York Heart Association.

for transplantation if their life expectancy is 2 to 3 years from the projected transplantation date.

Recipient Selection

Lung transplantation has been performed for nearly all conditions that result in severe isolated lung disease. The most common indications are chronic obstructive pulmonary disease, primary pulmonary hypertension, cystic fibrosis, and idiopathic pulmonary fibrosis. Recipient candidates should be carefully selected because of the significant risk of perioperative and postoperative morbidity and mortality and a limited number of donor organs. The *ideal patient* should be healthy enough to go through surgery safely with the least postoperative complications (both immediate and long term), yet sick enough to justify the considerable risks and expense of the procedure. Every patient is, therefore, required to undergo an extensive evaluation to determine transplant candidacy. This includes (1) a detailed history and physical examination; (2) blood, urine, and skin testing for latent infections or organ dysfunction; (3) cardiac and pulmonary function testing; (4) thoracic imaging by radiograph and computed tomography scan; and (5) a careful psychosocial assessment.

Every transplant center has its own specific guidelines regarding recipient selection. General consensus exists, however, regarding some conditions felt to be important in affecting short- and long-term outcome of transplant recipients. Absolute contraindications to transplantation include (1) human immunodeficiency virus (HIV) infection; (2) extrapulmonary, irreversible major organ dysfunction (e.g., concomitant renal or liver disease); however, patients with irreparable cardiac disease who are otherwise suitable candidates can be considered for heart-lung transplant; (3) hepatitis B antigenemia; and (4) hepatitis C infection, especially with histologically proved liver

disease. Most centers also consider the following characteristics to be relative contraindications to transplantation:

1. Older age, because older patients tend to have lower survival after lung transplantation (in general, ≤65 years for single lung transplant; ≤60 years for double lung transplant; and ≤55 years for heart-lung transplant). Chronological and biological or functional age can differ significantly in individuals and some centers are willing to consider patients above these age limits.
2. Preoperative severe osteoporosis has been associated with increased long-term morbidity and can compromise the objective of lung transplantation in improving the quality of life in recipients.
3. Steroid use is no longer an absolute contraindication because of improvement in surgical techniques in airway anastomosis; many centers now accept patients taking up to a daily dose of 10 to 20 mg prednisone.
4. A history of recent neoplasm, especially within the past 2 years, represents a significant risk of tumor recurrence. The actual disease-free interval will depend on the type of tumor and the associated risk of recurrence. Five-year documented disease-free interval may be more suitable in cases where neoplasm presents at a more advanced stage.
5. Many centers will put patients with active infection on hold, until the condition is treated. The presence of certain organisms (e.g., *Burkholderia cepacia* and pan-resistant *Pseudomonas* species) has been associated with adverse outcome, whereas colonization by *Aspergillus* or nontuberculous *Mycobacterium* does not appear to have an impact on mortality.
6. Severe musculoskeletal disease (e.g., severe kyphoscoliosis) can increase intraoperative difficulty and perioperative complications.
7. Ventilator dependence for any reason at the time of transplant has been associated with higher postoperative mortality.
8. Previous thoracic surgery, pleurodesis (especially by mechanical means), and pleurectomy all increase surgical difficulties and operative risks.
9. Extreme body weights (±20% of ideal body weight) is associated with worse outcome. Aggressive approaches, including dietary restriction or placement of a feeding tube, are often necessary for transplantation to be considered.
10. High levels of HLA-typed lymphocyte panel (panel reactive antibodies), usually from previous blood transfusion or pregnancy, can predispose patients to hyperacute rejection after transplantation. Strategies such as pretransplant HLA typing, plasmapheresis, or treatment with immunoglobulins have been used, although the efficacy is not known.
11. Psychosocial problems (e.g., recent or current substance abuse), history of noncompliance, and poorly controlled major affective disorders should be resolved before listing. Most centers require patients with a history of substance abuse to undergo at least 6 months of a supervised abstinence program. Refusal of blood products, as in the case of a Jehovah Witness, is usually considered a significant contraindication. Finally, all patients should have access to a much-needed social support network who are willing to participate in the complicated post-transplant care routine after discharge.

Pretransplant Follow-Up

Patients should be followed at regular intervals and transplant physicians must work closely with referring physicians to ensure that patients remain suitable transplant candidates. Because of the specific needs of pretransplant care and long waiting time, transplant physicians play an increasingly active role in patient care once they are listed. It is not unusual for patients to be placed on hold temporarily when, for instance, extreme body weight changes are needed or when patients require temporary mechanical ventilation. Other patients can develop conditions after listing that make transplantation unacceptable, such as airway colonization by *B. cepacia* in patients with cystic fibrosis. Conversely, patients can become *too healthy* for transplantation, as in some patients with primary pulmonary hypertension who receive long-term prostacyclin therapy. Health maintenance is an important part of pretransplant care to ensure optimal health before surgery. This includes yearly dental, eye, and gynecologic examinations, and up-to-date immunization for influenza, pneumococcus, hepatitis B, and

tetanus. Some transplant physicians will initiate aggressive pretransplant treatment of osteoporosis in high-risk patients, such as those on long-term steroid treatment and patients with cystic fibrosis.

Donor Selection

It is clear that proper donor selection and organ preservation improve transplant outcome. Potential recipients are matched with donors according to their ABO blood group and lung size. In theory, donors with blood type O may be considered as *universal donors*, although this can present potential issues of fairness with organ distribution. The choice between matching cytomegalovirus (CMV) status versus prophylactic anti-CMV treatment depends on institutional practice. Donor organs are routinely evaluated for function and to exclude active or latent infections. General guidelines for lung donation include age 65 years or less, no significant history of lung disease or smoking, normal chest radiograph, good lung compliance and oxygenation, and normal gross and bronchoscopic appearance. The use of *marginal donor* lungs is currently being evaluated.

Type of Transplantation Procedures

Four types of lung transplantation are done: single lung (SLT), bilateral (sequential) lung (BLT), heart-lung (HLT), and living donor transplantation. The type of transplantation performed depends on the underlying disease, associated conditions (e.g., previous thoracic or pleural surgeries), and institutional practice. Because of the limited number of suitable donors, SLT is preferred whenever feasible. It is also technically the most simple and, unlike other types of transplantation, can usually be performed via a thoracotomy without cardiopulmonary bypass. The disadvantages of SLT are that the recipients are left with one diseased lung, and patients generally have poorer results on pulmonary function testing even after recovery. Practically, however, patients with successful SLT have little functional disability in almost all normal daily activities.

Bilateral lung transplantation is performed through an anterior thoracosternotomy and is usually reserved for patients at risk of recurrent pulmonary infections if a native lung remains behind. It, therefore, is recommended for patients with cystic fibrosis or generalized bronchiectasis. Evidence also suggests that patients with primary pulmonary hypertension may have a better long-term outcome after BLT, compared with those who receive SLT. The perioperative management of patients with primary pulmonary hypertension after BLT appears to be simpler, because of decreased intraoperative hemodynamic disturbances and better pulmonary perfusion distribution. BLT for lymphangiomyomatosis remains controversial at this stage, with some data suggesting more favorable long-term results with BLT over SLT.

Because of the use of SLT and BLT, the incidence of HLT has decreased dramatically. HLT is done via a median sternotomy approach and is reserved mostly for patients with end-stage lung disease who have irreparable cardiac conditions, as is the situation in some cases of Eisenmenger's syndrome.

Because of the lack of donors, living donor transplantation has become increasingly popular. Most have been performed on pediatric patients with cystic fibrosis, with the donors being close family members. Two donors are required, each donating the lower lobe of one lung (right lower lobe and left lower lobe) to the respective chest cavity of the recipient. This procedure has the advantage of allowing extensive donor evaluation and can potentially improve HLA matching. Criteria for living donor transplant recipients should be the same for other types of lung transplantation and the procedure should not be performed as a *rescue* operation for patients *in extremis*. Aside from an increase in technical difficulties, ethical considerations are relevant to subjecting two healthy adults to a surgery that does not directly benefit their own health. To date, no deaths have resulted from living lung donation and preliminary results suggest that living donor transplantation may be a reasonable option in selected patients.

Post-transplant Management

Most centers use a three-drug immunosuppressive regimen that begins immediately before, or just after, surgery. A typical combination includes (1) cyclosporin or tacrolimus; (2) azathioprine or mycophenolate mofetil; and (3) prednisone. Induction therapy with

a cytolytic agent such as OKT-3 monoclonal antibodies or antithymocyte antibodies might be added during the first week after transplantation. Immediate complications after transplantation include bleeding, bronchial anastomosis dehiscence, reimplantation pulmonary edema, acute rejection or graft failure, and infection. Because mortality is highest in the first year after lung transplantation, frequent follow-ups are required during this period. Lung function normally improves gradually after transplantation and plateaus about 3 months after surgery.

Besides graft failure, bacterial infection, especially by *Pseudomonas* species, is the most common cause of death during the first 3 months after transplantation, and it continues to be a significant problem throughout the life of the recipients. Fungal infections, predominately from *Candida* and *Aspergillus* species, can occur both early and late after lung transplantation and should be treated aggressively. With the advent of oral antifungal agents, many centers now empirically treat patients who have evidence of fungal airway colonization, both before and after transplantation. Prophylactic antiviral therapy after transplantation may reduce infections from viruses such as CMV.

Acute lung rejections occur most commonly in the first year but can occur several years after transplantation. The clinical presentation is similar to that of pneumonia and treatment is often effective with short courses of high-dose steroids. Bronchoscopic examinations with or without transbronchial biopsies are usually required to differentiate between infection and acute rejection.

Chronic allograft rejection, manifested histologically as obliterative bronchiolitis, occurs in 34% to 41% of patients and usually presents with progressive shortness of breath and evidence of airflow obstruction on lung function test. It usually occurs months to years after transplantation and is often preceded by an episode of infection or acute rejection. Unlike acute rejection, chronic rejection is often refractory to treatment and some centers advocate routine surveillance bronchoscopic examinations for early disease detection and treatment. Retransplantation remains a controversial option for patients with severe irreversible allograft failure.

Most other long-term complications after transplantation are related to the use of immunosuppressive therapy. Osteoporosis, renal insufficiency, myelosuppression, and malignancy (especially skin cancer and lymphoproliferative disease) occur commonly after lung transplantation. Narrowing of airways at the site of anastomosis is common and may require bronchoscopic dilatation and stent placement. A high index of suspicion for these complications will enable their early detection and timely treatment.

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A high incidence of CMV pneumonitis was seen after transplantation, especially in CMV positive donors. Only one third of cases of CMV pneumonitis had chest radiograph changes.

VII. CONGENITAL AND PEDIATRIC LUNG DISEASE

71. PULMONARY MANIFESTATIONS OF SICKLE CELL DISEASE

Stephen P. Bradley

Sickle cell disease (SCD) is a clinical syndrome common to a group of hemoglobinopathies in which the primary defect is the tendency of deoxygenated hemoglobin S to form large polymers that deform erythrocytes, blocking capillary blood flow and causing tissue ischemia. Pulmonary involvement is common and often severe; approximately 15% to 43% of patients with sickle cell anemia develop the acute chest syndrome. Patients with SCD who survive into adulthood are at risk of developing sickle chronic lung disease, which is associated with marked disability and decreased survival.

Patients with SCD, particularly children, are at increased risk of infection for several reasons. Functional asplenia occurs early in the course (before recurrent infarction leads to involution of the organ), resulting in poor bacterial clearance from the blood stream. In addition, patients with SCD may have defects in polymorphonuclear leukocyte function (defective degranulation and intracellular killing) and deficient serum opsonizing activity, leading to recurrent infections. In the lung, microvascular occlusion probably leads to local impairment of phagocytic activity. As a result of these defects in immune function, the relative risk of pneumonia is 20 to 100 times greater in children with SCD.

Streptococcus pneumoniae is the most frequently identified cause of pneumonia in SCD, accounting for 58% of such cases in children less than 2 years of age, and 25% in patients older than 10 years of age. *Haemophilus influenzae* is isolated in approximately 18% of patients; other important causes of pneumonia are *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, *Mycoplasma* species, and other gram-negative organisms. Pneumonia, particularly with bacteremia, is an important cause of death in children with SCD before the age of 4 years. Thereafter, the decline in the incidence of pneumonia and, particularly, bacteremic pneumonia (14% in children < 2 years vs 1.8% in patients > 10 years) is attributed to the development of specific antibodies to the offending organisms.

In general, the clinical presentation of pneumonia in patients with SCD is not unique; however, the severity of the illness tends to be greater and the response to therapy is slower, than in otherwise healthy individuals. A combination of third-generation cephalosporins and macrolide therapy is the most common initial empiric therapy; however, the addition of antistaphylococcal therapy should be considered in some patients.

The acute chest syndrome (ACS) is usually defined as the development of fever, cough, and chest pain in patients with SCD. Other common symptoms include dyspnea, chills, sputum production, and, occasionally. hemoptysis, all of which increase in frequency with age. The physical examination may be normal in about one third of patients with ACS; rales are the most common abnormal finding. Initial chest roentgenography is normal in up to 46% of cases; however, most patients will develop focal or diffuse pulmonary infiltrates or atelectasis within 1 to 2 days. Pleural effusions are seen in 15% of cases (31% of adults and 3% of young children).

Although the term *acute chest syndrome* was originally used to describe patients in whom a noninfectious cause for their presentation was postulated, in the clinical realm distinguishing infectious from noninfectious causes of the above-described signs and symptoms is difficult. The problem is clearly worsened by the insensitivity of currently available diagnostic tests for pneumonia. For this reason, many authors include both groups in their studies of ACS, considering infection as the underlying cause of the syndrome only if pneumonia is bacteriologically proved. Characteristics that suggest a noninfectious cause include (1) upper or middle lobe disease; (2) associated pain crisis; (3) older age; (4) negative sputum smears and sputum or blood cultures for usual bacterial pathogens; (5) rapid improvement in chest roentgenography (<72 hours); and (6) associated neurologic symptoms.

Acute chest syndrome is one of the most frequent reasons for hospitalization in the SCD. It occurs in 30% to 45% of patients with SCD. In the largest study, approximately 55% of patients who experienced ACS had a single event over their lifetimes, and only 9% had experienced five or more episodes. Risk factors for the development of ACS include young age (many of whom have infection identified as the cause), low levels of hemoglobin F, elevated hematocrit, and high leukocyte count. Among the sickle hemoglobinopathies, SS disease confers the greatest risk, followed by Sβo-thalassemia, sickle cell disease, and Sβ+-thalassemia; α-thalassemia has no effect on the risk of developing ACS.

An ACS-like syndrome has been reported in patients with the sickle trait, but its occurrence is rare. Among patients with SS disease, haplotype may also play a role. Thus, patients with the Central African Republic haplotype frequently have severe, progressive disease (including pulmonary disease); those with the Senegal haplotype have the lowest incidence of ACS (and longest survival); and those with the Benin variant have an intermediate risk.

Several different causes of ACS have been proposed, and each probably plays a role in different clinical situations. As noted, young children often have an infectious organism isolated from blood or sputum. In addition, the incidence of ACS in children (and less so in adults) follows a seasonal pattern, with the greatest incidence in the fall and winter, suggesting a causative role for respiratory tract infections by otherwise poorly virulent organisms such as viruses or chlamydia.

Lung infarction, from a variety of causes, is probably also an important cause of ACS. The deoxygenated blood entering the pulmonary circulation is susceptible to sickling, making the lung particularly vulnerable to *in situ* microvascular thrombosis and tissue infarction. Local ischemia, as would occur in the setting of pneumonia or atelectasis, can accelerate this process. Large vessel pulmonary embolism resulting from deep vein thrombosis probably occurs with about the same frequency as it does in the general population, and is not considered to be a major cause of ACS. On the other hand, several lines of evidence suggest that bone marrow embolization to the lung, occurring as a result of bone infarction during an acute pain crisis, is an important cause of ACS. A syndrome of fatal fat embolism occurring in pregnant women with SCD is well described. Autopsies of these patients disclose necrotic marrow fragments occluding the pulmonary arteries. In addition, an autopsy study of patients with advanced SCD disease dying from any cause disclosed bone marrow fragments in the pulmonary circulation in 13%. Many of the patients with marrow fragments had died suddenly and without another explanation, and had a history of a recent episode of ACS. Clinically, acute pain (bony) crisis often precedes the onset of ACS by several days, and bone scintigraphy performed during ACS frequently demonstrates evidence of acute long bone infarction; occasionally, the bone involvement documented scintigraphically is asymptomatic. A study of bronchoalveolar lavage fluid from patients with ACS demonstrated the presence of a high percentage of lipid-laden alveolar macrophages, similar to the finding in fat embolism syndrome secondary to traumatic long bone fracture. As in the fat embolism syndrome, patients with ACS had a high incidence of neurologic abnormalities (50% had depressed consciousness, seizures, or focal neurologic signs on examination), adding further evidence that marrow embolization is a common cause of ACS.

Thoracic bone infarction is another probable cause of ACS. Infarction involving the ribs, sternum, or thoracic spine can be demonstrated on bone scintigraphy in some patients. Local soft tissue reaction involving the chest wall, pleura, and subpleural lung, as well as atelectasis secondary to splinting, could lead to local ischemia, erythrocyte sickling, and pulmonary infiltrates.

Treatment of ACS is largely supportive. Antibiotics directed against appropriate pulmonary pathogens are usually given, as infection is difficult to exclude. Oxygen is administered to correct hypoxemia and to decrease sickling of deoxygenated blood. The degree of hypoxemia is frequently out of proportion to the radiographic abnormalities. Intravenous hydration is given to decrease the rheologic effects of sickled red cells. Narcotic (and non-narcotic) analgesics are usually required to control pain and to minimize splinting and atelectasis. Simple transfusion is generally reserved for patients with significant anemia; exchange transfusion results in rapid improvement in arterial hypoxemia but the high risk of transfusion reactions in SCD patients prevents its

routine use. One group of patients, however, clearly benefits from transfusion therapy. A 10% risk of postoperative ACS is seen in patients with SCD undergoing surgical procedures under general anesthesia. Preoperative transfusion to a hemoglobin level greater than 10 g/dl decreases this risk substantially. Diligent use of incentive spirometry has been shown to decrease the risk of pulmonary complications (development of pulmonary infiltrates or atelectasis) and to shorten hospitalization in patients with ACS secondary to thoracic bone infarcts.

Despite aggressive support, up to 25% of deaths in SCD are attributed to ACS. The risk increases with age; whereas the overall mortality during an episode of ACS is 1.8%, in adults it is 4.3%. Other risk factors for death include respiratory failure developing within 48 hours of presentation, bacterial sepsis, and associated pain crisis. However, several authors have noted that the initial presentation can be a poor predictor of outcome; some patients presenting with relatively mild symptoms rapidly develop progressive pulmonary infiltrates and intractable respiratory failure. In some patients, overwhelming infection is probably the cause of death; in others, it has been suggested that free fatty acid released from areas of bone marrow infarction results in pulmonary vascular injury and the acute respiratory distress syndrome.

Patients who survive repeated episodes of ACS are at risk of developing sickle chronic lung disease (SCLD). SCLD is characterized by progressive dyspnea with exercise limitation, and chest pain of increasing severity. Pulmonary function testing reveals hypoxemia, low lung volumes, and a restrictive ventilatory defect. A diffuse increase in interstitial markings is seen on chest roentgenography; however, thin section computed tomography (CT) shows no evidence of interstitial fibrosis or ground glass infiltrates. The radiographic abnormalities are caused by subpleural scarring, patchy interlobular septal thickening, dilated secondary pulmonary lobules, traction bronchiectasis, and, perhaps, from vascular engorgement secondary to high output congestive heart failure. Electrocardiogram demonstrates right ventricular hypertrophy, and echocardiography confirms pulmonary hypertension. Myocardial infarction (without significant coronary artery disease), which is common as a terminal or preterminal event, may be caused by a combination of anemia, hypoxemia, sickling, biventricular thickening, and high cardiac output. The average age at diagnosis is approximately 25 years. However, careful evaluation of at-risk patients reveals that pulmonary physiologic abnormalities are demonstrable for several years before the onset of severe symptoms. These patients progress through a series of stages, initially marked by recurrent chest pain and cough, with mild restriction on pulmonary function testing, which develops into florid cor pulmonale (stage 4), and eventually results in death. The average time from the first detectable defect until death is just over 7 years. Although a clustering of ACS episodes occurring before the onset and throughout the course of SCLD is well documented, the mechanisms by which the acute events lead to irreversible lung damage are poorly understood. Therapeutic interventions have not yet been able to change the outcome of this devastating disease. Some patients have been reported to have an improved sense of well-being from chronic transfusion therapy to maintain a hemoglobin S level below 30%.

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72. CYSTIC FIBROSIS

Douglas J. Conrad

Cystic fibrosis is a systemic disease characterized by exocrine gland dysfunction that commonly results in sinusitis, progressive inflammatory bronchitis, bronchiectasis, pancreatic malabsorption, and protein-calorie malnutrition. Other frequently encountered manifestations include hemoptysis, pneumothorax, cirrhosis secondary to biliary stasis, pancreatitis, azoospermia, and obstructive colonopathy. In the past, patients with cystic fibrosis rarely survived through childhood, and were cared for almost exclusively by pediatricians. However, because of more aggressive treatment and newer therapies, the current median age of patients with cystic fibrosis is approximately 30 years. In addition, mild or atypical forms of cystic fibrosis can present for the first time during adulthood. For these reasons, primary care providers and adult pulmonologists are increasingly involved in the diagnosis and management of patients with cystic fibrosis.

The gene and the most common mutations associated with the disease were identified in 1989. These studies also provided the initial characterization of the cystic fibrosis gene product, a protein termed the *cystic fibrosis transmembrane conductance regulator* (CFTR). Cystic fibrosis is inherited in an autosomal recessive pattern. Mutations in the cystic fibrosis gene are common, but the incidence varies significantly among different ethnic populations. The estimated carrier frequency in normal populations varies from 1:29 in North American whites, to 1:90 in Asian-Americans. The disease occurs in 1 of 3300 North American whites, 1 of 15,300 African-Americans, 1 of 9500 Hispanics, and 1 of 32,000 Asian-Americans. Carriers of a single mutated CFTR allele are asymptomatic and have a normal prognosis.

The CFTR protein is located primarily on the apical membranes of epithelial cells of the respiratory, hepatobiliary, and pancreatic tracts, as well as in the crypts of the large intestine and sweat gland ducts. It forms a large pore in the cell membranes, which functions as a chloride channel. Dysfunction of the ion transport properties of CFTR are believed to be responsible for the pulmonary manifestations of cystic fibrosis. The ion transport properties of airway epithelial cells are critical for maintaining the hydration and normal function of the airway lining fluid. When these processes

are disturbed, the mucociliary clearance mechanism is diminished and bacteria chronically colonize the airways. In addition, recent data suggest that the abnormal ion concentration of the epithelial lining fluid impairs the immune response by inactivating antimicrobial peptides normally produced by airway epithelial cells.

Bacterial colonization of the airways leads to bronchiectasis, airway obstruction, and, eventually, respiratory failure through a self-perpetuating cycle of inflammation and decreased airway clearance. The bacteria stimulate neutrophil recruitment into the airways. The neutrophils are ineffective in clearing the infection and die, leaving large quantities of DNA and proteases in the airways. The DNA dramatically increases airway secretion viscosity, further impairing airway clearance. The neutrophil proteases stimulate submucosal gland hypertrophy and secretion, and eventually result in a breakdown of the airway architecture and bronchiectasis. The bronchiectasis is progressive and leads to respiratory failure in 85% of patients with cystic fibrosis. The pathophysiology of cystic fibrosis in the gastrointestinal tract is less clear but involves pancreatic duct obstruction that leads to destruction of the pancreas and results in protein-calorie malnutrition and diabetes mellitus.

Diagnosis and Evaluation

Patients with cystic fibrosis can present with a wide variety of respiratory and gastrointestinal complaints that are usually evident in childhood. The more common manifestations include nasal polyps, sinusitis, bronchospasm, recurrent bronchitis or pneumonia, airway colonization of mucoid *Pseudomonas aeruginosa*, steatorrhea, pancreatic malabsorption, meconium ileus, failure to thrive, rectal prolapse, distal intestinal obstructive syndrome, and hepatic cirrhosis (focal biliary cirrhosis). Undiagnosed adults frequently present with recurrent bronchitis (in a nonsmoker), asthma associated with the radiographic evidence of diffuse bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA), airway colonization with atypical mycobacteria or mucoid *P. aeruginosa*, cirrhosis, idiopathic pancreatitis, or male infertility.

Typically, the physical examination will disclose nonspecific findings. Acute or chronic sinusitis with nasal polyps is common. Chest examination reveals an increase in the anteroposterior diameter, with decreased diaphragmatic excursion. Diffuse rales, rhonchi, and bronchospasm are evident in most patients, although breath sounds are occasionally normal. Digital clubbing is frequent. Most patients have pancreatic insufficiency and, thus, have some degree of protein-calorie malnutrition.

Taken individually, the findings on history and physical examination are nonspecific; however, the particular combination of signs and symptoms of the typical presentation are specific for cystic fibrosis. Only cystic fibrosis presents with the following pattern: (1) sinusitis; (2) bronchitis or bronchiectasis; (3) pancreatic malabsorption with malnutrition; (4) obstructive colonopathy; and (5) male infertility. Although ciliary dysfunction (Kartegener's syndrome) or immunoglobulin deficiencies mimic some of the pathophysiologic consequences, they are not usually associated with gastrointestinal symptoms. In patients with mild or atypical clinical presentations, laboratory confirmation is helpful to confirm the diagnosis early in the disease process.

The sweat chloride test remains the standard in the laboratory diagnosis of cystic fibrosis. This test should be performed by experienced laboratory personnel. Pilocarpine iontopheresis is used to stimulate secretion of sweat, which is collected, weighed, and analyzed for its chloride and sodium concentrations. A chloride concentration greater than 60 mEq/L is diagnostic of cystic fibrosis, with most findings falling in the 90 to 120 mEq/L range. Positive or indeterminate (values between 40 and 60 mEq/L) should be repeated at least once.

Since the identification of the gene for cystic fibrosis in 1989, more than 800 disease-causing mutations have been identified. Most laboratories screen for 40 of the most common mutations, which account for nearly 90% of North American patients with cystic fibrosis. The most common mutation is delta F508, which accounts for nearly 66% of the mutated alleles in the North American cystic fibrosis populations. Homozygosity for delta F508 is the most common genotype in this population and occurs in approximately 50% of patients. Tests for these mutations may be helpful in diagnosing atypical or mild presentations of the disease.

Pulmonary function testing in the setting of cystic fibrosis is frequently abnormal but not specific. Spirometry reveals airway obstruction and lung volumes frequently

demonstrate air trapping. Pulmonary function tests, however, are useful for following the course of the disease or monitoring the effectiveness of therapy. The data can be used to complement assessments of the patient's clinical performance.

Chest radiographs usually show changes consistent with bronchiectasis or demonstrate evidence of mucus plugging or atelectasis. They may also identify pneumonia, pneumothorax, or manifestations of bronchial arterial bleeding. Bronchiectasis is best evaluated on thin-cut thoracic computed tomography scanning, which has replaced bronchography.

Blood counts and serum chemistries can help identify some common complications of the disease. White blood counts are frequently normal or slightly elevating during exacerbations, but rise much higher during pneumonia or steroid therapy. Hemoglobin levels may help explain unexpected dyspnea, because many patients are anemic because of chronic inflammation or gastrointestinal blood loss. Serum chemistries can be affected if the patient has renal tubular dysfunction from aminoglycoside use or chronic respiratory acidosis or uses diuretic therapy. Liver-associated enzymes are frequently elevated with a cholestatic pattern, but are typically no greater than three times normal. In patients with abdominal pain, serum lipase and amylase levels may be helpful to rule out pancreatitis. Prealbumin levels can help guide nutritional therapy. Hemoglobin A1c and fasting blood glucose levels are obtained in older patients with cystic fibrosis to monitor glucose intolerance. Finally, serum levels of vitamins A, E, and D are helpful to monitor the success of supplementing the fat-soluble vitamins.

Chronic Management

Management of cystic fibrosis is focused on (1) maintaining optimal nutritional status; (2) promoting airway clearance of inflammatory cells; (3) decreasing bacterial colonization; and (4) minimizing the impact of respiratory and gastrointestinal complications.

Chronic sinusitis is evident in most patients with the disease; symptoms are managed initially with antibiotics and topical steroids. Although conservative management can be helpful, many patients are eventually referred for surgical polypectomies, sinus antrectomies, and tissue debridement. This aggressive therapy frequently relieves symptoms and, in some cases, is associated with an improvement in pulmonary function.

Management of the progressive bronchitis and bronchiectasis focuses on diminishing airway inflammation and promoting airway clearance. Antibiotics are used to decrease the level of bacterial colonization. Chronic use of antibiotics targeting *Staphylococcus aureus* in colonized patients is safe and may be helpful. Stronger clinical research supports the use of inhaled antibiotics, particularly tobramycin. Recent studies have shown that inhaled tobramycin (3000 mg, twice daily, every other month) is safe, improves pulmonary function, and decreases the use of intravenous antibiotics. Other antibiotics that have been used as inhaled medications include gentamicin, colistin, and the β-lactam antibiotics. In general, inhaled antibiotics are best used as prophylactic therapies and are less useful during acute exacerbations.

Several pharmacologic therapies may improve airway clearance and reduce airflow obstruction. The concentration of DNA in respiratory secretions of patients with cystic fibrosis is high and has been shown to dramatically increase the viscosity of the sputum and to impair its clearance. Aerosolized deoxyribonuclease (DNase), a pancreatic-derived enzyme that degrades DNA, may be inhaled to diminish the effect DNA has on respiratory secretion viscosity. Clinical studies have demonstrated improvement in pulmonary function, decreased use of antibiotics, and subjective improvement in symptoms with inhaled DNase.

Airway clearance and airflow obstruction in patients with marked bronchospasm can be improved with corticosteroids and bronchodilators. The use of steroids in cystic fibrosis is controversial largely because of the risk of adverse effects. They are generally not used in the chronic outpatient management of patients with this disease, but are used in selected patients with severe lung disease and bronchospasm. Inhaled bronchodilator therapy with a β-agonist or ipratropium is helpful for many patients to relieve symptoms secondary to bronchospasm and to facilitate airway clearance. Oral bronchodilators including theophylline and β-agonist preparations are used in the pediatric setting where inhaled therapies are sometimes not effective, in patients who are not compliant with inhaled therapy, and as an adjunct to optimally delivered inhaled therapy.

Selected patients with prominent airway hyperreactivity may improve significantly with inhibitors of the 5-lipoxygenase pathway, particularly the newer leukotriene receptor antagonists. Chronic use of nonsteroidal anti-inflammatory medications, specifically ibuprofen, has been demonstrated to preserve lung function. These effects were most prominent in children and in patients with mild lung function abnormalities.

Chest physiotherapy is the major mechanical means of augmenting airway clearance. This is typically delivered manually or with a mechanical percussor two to four times a day. Other airway clearance techniques, such as autogenic drainage, positive expiratory pressure masks, and flutter valves, are helpful. A newer therapy uses a vest attached to a pressure oscillator to generate airway-shearing forces and dislodge inspissated secretions.

Many providers encourage patients to perform strenuous aerobic exercise daily. Exercise improves cardiovascular conditioning, promotes airway clearance, and, importantly, benefits patients psychologically. Patients who perform routine aerobic exercise are also able to notice a decline in their performance, which can be an early indicator of pulmonary illness requiring therapy.

Lung transplantation is an option for some patients with severely depressed lung function whose lifestyles have been significantly limited by the disease. Lung transplant candidates are carefully selected, with consideration given to other medical comorbidities, psychosocial support, and patient motivation. In most centers, the mortality rate in patients with cystic fibrosis after lung transplant is similar to that of other lung transplant patients. Most centers that perform lung transplantation for patients with cystic fibrosis report a 1-year survival rate of approximately 70% to 80% and a 3-year survival rate of 50%.

Other commonly encountered pulmonary complications that are frequently managed on an outpatient basis include allergic bronchopulmonary aspergillosis (ABPA) and airway colonization with atypical mycobacteria. ABPA is a hypersensitivity reaction to aspergillus in the airway, which has been demonstrated in 5% to 20% of patients with cystic fibrosis. Atypical mycobacteria frequently colonize the airways, causing no harm. On occasion, however, these mycobacteria can invade the lung parenchyma, causing progressive airway destruction and volume loss. Standard therapy has not been established for invasive disease but it frequently requires multiple drug therapy (e.g., clarithromycin, ethambutol, and rifampin) for prolonged periods of time.

Pancreatic malabsorption and protein calorie malnutrition should be aggressively managed. Thorough reviews of daily caloric intake and monitoring of body weight are important to maintaining nutritional goals. Intermittently evaluate protein stores. Fat-soluble vitamins (vitamins A, D, E, and K) are not readily absorbed through the gastrointestinal tract of patients with cystic fibrosis. These vitamin levels should be monitored annually and dietary supplements provided. Adequate pancreatic enzyme replacement is the key to maintaining the nutritional status of the patients and to avoid the symptoms of pancreatic malabsorption. As a general rule, most patients who have insufficient pancreatic function require between 1000 and 2000 U/kg body weight per meal of lipase activity. In patients who are compliant with the nutritional regimen but whose body weight remains less than 80% of the ideal body weight, the oral diet should be augmented with nocturnal gastrostomy tube feedings of nutritional supplements.

Occasionally patients with cystic fibrosis will develop an obstructive colonopathy such as meconium ileus or distal intestinal obstructive syndrome. Frequently, they will complain of constipation and right-sided abdominal pain. This abdominal pain needs to be distinguished from peptic ulcer disease, cholelithiasis, pancreatitis, colitis, or appendicitis. Initial management should include the administration of pancreatic enzymes, along with mild laxatives and an increase in dietary fiber. Gastrografin enemas may help relieve the obstruction in some cases; surgery is rarely needed.

Inpatient Management of Complications

The most common reasons for hospital admissions are pulmonary exacerbations of infectious bronchitis. Patients that are not responding to outpatient therapy, including oral antibiotics, often present with worsening exertional capacity and diminished pulmonary function. Although home intravenous antibiotic administration is an option for treatment of pulmonary exacerbations in some patients, these patients must

be carefully selected. Those who are most likely to have successful outcomes with out-patient intravenous antibiotics typically have had good responses to antibiotics in the past, are very motivated, and have adequate support in the home. Inpatients are typically treated with two antibiotics targeting organisms observed in sputum cultures. In vitro sensitivity data may help guide the antibiotic selection; however, clinical improvement is frequently observed even when the cultured bacteria have demonstrated significant in vitro resistance. In most cases, patients are treated empirically with two antipseudomonal antibiotics and an antibiotic targeting *S. aureus* if it is present in the airways. In addition to antibiotics, patients typically receive aggressive chest physiotherapy four times daily. Pancreatic malabsorption is treated the same as it is in the outpatient setting.

The use of mechanical ventilation to treat respiratory failure is particularly controversial. All decisions regarding mechanical ventilatory support should be individualized. Some patients who are cooperative and motivated may respond temporarily to noninvasive ventilatory support. In general, patients who develop respiratory failure despite optimal treatment should not be mechanically ventilated because of the progressive nature of this disease. However, patients who have not received optimal therapy or who have respiratory failure secondary to reversible complications (e.g., hemoptysis, pneumothorax, and so on) should be considered for mechanical ventilation.

Massive hemoptysis (>250 ml/24 hours) is not unusual in patients with severe lung disease from cystic fibrosis. Most patients can be treated conservatively, using supportive measures such as intravenous antibiotics, oxygen supplementation, temporary suppression of cough, avoidance of chest physiotherapy during active bleeding, transfusions of platelets or packed red blood cells, when appropriate, and the correction of any clotting abnormalities with either vitamin K or fresh, frozen plasma. Occasionally, these measures are inadequate because of progressive respiratory failure or ongoing bleeding. In these cases, medical stabilization should be followed with bronchial arterial embolization which usually controls active bleeding quickly. Surgery is very rarely needed for control but should be considered if embolization does not control life-threatening bleeding and the patient is an adequate surgical candidate.

Pneumothorax occurs frequently in patients with severe lung disease caused by cystic fibrosis. Conservative therapy with oxygen supplementation, antibiotics, and bronchodilators is usually successful in patients with small asymptomatic, pneumothoraces. In patients with larger, symptomatic or nonresolving pneumothoraces, a more aggressive approach is warranted. A chest tube should be placed under fluoroscopy or by an experienced individual because the pleural space can be complicated by cystic fibrosis. Chest tube drainage is frequently successful in re-expanding the lung and allows the option of chemical pleurodesis. Surgical pleurodesis is rarely needed.

Developing Therapies

Cystic fibrosis is an area of active clinical research. Future therapeutic strategies target many of the pathophysiologic steps outlined above. Some of the more promising areas of research are aimed at reversing the ion transport abnormalities in the epithelium using other treatments, such as uridine triphosphate (UTP) and amiloride. Other approaches attempt to boost CFTR activity in mutations that have residual activity. Finally, gene therapy offers a chance of curative therapy in selected patients, or of arresting the decline in pulmonary function in patients with existing disease. In the future, successful therapy for cystic fibrosis is more likely to take a multidisciplinary approach using multiple therapies targeting the pathophysiologic process at several areas.

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73. NEONATAL RESPIRATORY DISTRESS SYNDROME

Frank L. Mannino

Respiratory distress syndrome (RDS), or hyaline membrane disease, in a sense is not a true disease, but a developmental abnormality in a prematurely born infant forced to air breathe before the maturation of the respiratory system. Recent developments in treatment, especially surfactant replacement therapy, have dramatically altered the clinical course, morbidity, and mortality of this disease, such that infants above 1000 g birth weight now have a 95% survival rate.

Approximately 50,000 infants per year are affected by RDS. It continues to be one of the leading causes of death in premature infants, although the mortality rate dropped significantly with the introduction of surfactant treatment in the late 1980s and early 1990s. The incidence increases with decreasing gestational age. Normally, the lungs are mature at 35 to 36 weeks' gestation, which makes RDS uncommon in infants above this gestation unless the mother is affected by other conditions such as diabetes. The incidence at earlier gestations also varies depending on the local population; concurrent maternal, placental, and fetal conditions; and the treatment received by mothers who are in premature labor. The incidence reaches 90% in infants under 26 weeks' gestation and drops to less than 20% at 35 weeks' gestation. The prevalence in larger infants has been decreasing because of improvements in obstetric practice that have reduced the number of infants born at 34 to 36 weeks' gestation with immature respiratory systems who were incorrectly thought to be at term.

The morbidity and mortality of RDS has decreased with improved general care and the introduction of surfactant replacement therapy. However, this has led to a new category of extremely low birth weight infants (*micro preemies*) of 24 to 26 weeks' gestation (500–800 g birth weight), who are at the borderline of adequate pulmonary maturation to sustain life. This new group of infants continues to have a high incidence of

long-term morbidity. The long hospitalization (80–120 days) can have an adverse affect on resource utilization. Also, for some of the infants destined to die, the time to death, previously 1 to 2 days of age, has increased.

Infants presenting with RDS are premature and have early evidence of respiratory distress in the first hours of life, including tachypnea, inspiratory retractions (suprasternal, substernal, and intercostal), paradoxical seesaw respirations, inspiratory nasal flaring, and an audible expiratory grunt. In very premature infants, intubation and mechanical ventilation may be necessary in the delivery room because of poor transition to air breathing.

The course of classic RDS has been defined for infants who manage to survive without significant initial ventilatory treatment. In these infants, usually of 30 to 35 weeks' gestation, is seen progressive respiratory insufficiency with increasing need for supplemental oxygen. Pulmonary function testing reveals decreased lung compliance, low functional residual capacity (FRC), and greatly increased work of breathing. Respiratory symptoms maximize at 2 to 3 days with a recovery over the next 2 to 4 days coincident with endogenous surfactant production. Recovery is heralded clinically by the onset of a diuresis. With early surfactant replacement treatment, the course of RDS is radically altered; there is an immediate reduction in oxygen requirements and rapid weaning of mechanical ventilation. Many infants can be extubated by 12 to 48 hours of age except in cases of extreme prematurity or if concurrent problems exist.

The radiographs of patients with established RDS have a homogeneous ground-glass appearance with central and peripheral air bronchograms representing atelectasis of some terminal respiratory units around expanded respiratory bronchioles. (An x-ray study in the first hour of life in some infants may reveal just a hazy lung before the development of the air bronchograms.)

Infants who die shortly after birth may not show typical pathologic findings, but infants living longer reveal the typical eosinophilic-staining hyaline membranes from which comes the pathology-derived name of this syndrome, hyaline membrane disease. The hyaline membranes, which are in terminal bronchioles and alveolar ducts or primitive alveolar areas, represent a proteinaceous substance, presumably from respiratory wall damage and capillary leak. Such findings can exist in other severe respiratory diseases such as neonatal pneumonia and the adult respiratory distress syndrome.

The course of RDS can be complicated by pulmonary air leaks such as pneumothoraces and pulmonary interstitial emphysema. In extremely immature infants, intraventricular hemorrhage can occur because of anatomic immaturity and the physiologic instability of such infants. The ductus arteriosus may remain patent. Even in the early stages of RDS, lung inflammation is present, which can lead to *chronic lung disease* or bronchopulmonary dysplasia.

The pathophysiology of RDS represents a complex combination of developmental problems combined with the effect of air breathing on the immature respiratory system. The primary underlying problem is a deficiency in the quantity and molecular characteristics of the pulmonary surfactant. However, the immaturity is not related solely to the surfactant system. In most premature infants, only respiratory bronchioles and primitive alveolar ducts are present. The lung parenchyma is immature with decreased connective tissue and increased overall cellularity. These factors make the premature lung more stiff, with increased resistance to breathing. The respiratory pump is also immature; the floppy chest wall cannot maintain an FRC or generate adequate tidal volume in the face of a very noncompliant lung.

A third component is the persistent patency of the ductus arteriosus with the potential for a progressive left-to-right shunt. Although shunting can be right-to-left or bidirectional in the initial phase of the disease, an early left-to-right shunt with pulmonary overcirculation is usually present, adding to the pulmonary edema already existing.

Last of all, lung is damaged from spontaneous breathing and from the relative overdistention during mechanical ventilation. Direct damage has occurred to terminal bronchioles and alveolar linings and secondary damage to the cellular components of the airway from white cell migration and release of toxic compounds. Leak of serum proteins and edema fluid inactivates what little surfactant is present. If this process is severe or persists, the result is broncho-pulmonary dysplasia (BPD) or more commonly now, a mild form of chronic lung disease defined as oxygen need at 28 days of life (or 36 weeks corrected gestational age) with some chest radiographic abnormalities.

A lack of mature pulmonary surfactant is the primary cause of RDS. Pulmonary surfactant is a complex mixture containing approximately 80% phospholipids, 10% surfactant-related protein, and 10% neutral lipids (primarily cholesterol). Phosphatidylcholine is the major phospholipid, representing approximately 80% of the total phospholipid species. Of the phosphatidylcholine, 60% to 70% contains a saturated 16-carbon fatty acid (palmitic) on two of the three carbon glycerol backbones, resulting in dipalmitoylphosphatidylcholine (DPPC) or lecithin. The remainder of the phosphatidylcholine contains unsaturated fatty acids with primarily one double bond. Other phospholipids include phosphatidylglycerol (PG), representing approximately 10% of phospholipids in mature surfactant and, in lesser amounts, phosphatidylinositol and phosphatidylethanolamine.

Immature lungs not only have a reduced amount of surfactant present but also do not contain PG. There is an increased percentage of phosphatidylinositol to 35 weeks' gestation, which then decreases toward term. Because of the mixing of lung effluent with amniotic fluid, an indication of the maturity of the surfactant system may be obtained by analysis of the phospholipids or surfactant proteins in the amniotic fluid. The lecithin:sphingomyelin (L:S) ratio alone or combined with analysis of other phospholipids (*lung profile*) can fairly well predict lung maturity with a low false-positive rate. Although false-negative results can be high for this and other amniotic fluid tests for lung maturity, the indication for maturity is of greatest clinical significance.

Of the four described surfactant-related proteins, surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, and SP-D), only SP-B and SP-C have been shown to improve the surface active properties of the phospholipid-surfactant mixture. Although present in small amounts, they help lower the surface tension and help spread the surfactant film throughout the lungs. In fact, absence of SP-B is incompatible with life. Both SP-B and SP-C are present in organic solvent extracts of surfactant.

The surfactant is generated in type II cells, which represent a small percentage of the alveolar lining cells. It is concentrated in the characteristic lamellar bodies in the type II cells, then secreted into the alveolar space. A variety of transformations then take place, resulting eventually in a molecular surface film with hydrophobic fatty acid components on the gas side and hydrophilic phospholipid moieties on the aqueous subphase. The proteins play a role in the transport of the lipid and the formation and stabilization of this surface film. The half-life of surfactant in the neonatal lung can be several days or longer. However, the surfactant appears to recycle into the type II cell and back to the alveolar space many times during the half-life.

Although the primary function of surfactant is to reduce surface tension between air-liquid interfaces in the alveoli, pulmonary surfactant can play other major roles. These include a function in keeping the airways dry and patent from small amounts of fluid obstruction. The surfactant can also assist in mucociliary activity, further keeping peripheral small airways open. Finally, the mature, intact surfactant appears to have anti-inflammatory characteristics in the setting of chronic inflammation caused by infection.

Surfactant replacement therapy was attempted within 5 years of the 1959 Avery discovery of surfactant deficiency in RDS. However, the first surfactants used were primarily aerosolized lecithin alone. The combination of an incomplete surfactant, inadequate delivery techniques, and insufficient quantity led to poor results and surfactant replacement therapy was delayed for another 20 years until these problems were resolved. Currently four surfactant compounds are approved by the US Food and Drug Administration, with others in development.

Exosurf Neonatal (Glaxo Wellcome), approved in 1990, is a totally synthetic surfactant consisting of 85% DPPC as the phospholipid, 9% hexadecanol, an alcohol, and 6% tyloxapol, a detergent. The latter two components help in spreading and stabilizing the surface film. Survanta (beractant; Abbott Laboratories), approved in 1991, is a partially synthetic surfactant obtained from organic solvent extraction of minced bovine lung with added DPPC and palmitic acid, resulting in 90% phospholipids. Unlike Exosurf, SP-B and SP-C are present. Two additional surfactants containing these proteins were approved in 1999. They are Infasurf (calfactant; Forest Laboratories), an organic solvent extract of calf lung bronchioalveolar lavage and Curosurf (poractant alfa; Dey Laboratories), an organic solvent extract of minced bovine lungs further

purified by liquid-gel chromatography to remove neutral lipids. Other surfactants undergoing trials in the United States or approved elsewhere include Surfacten (Surfactant-TA; Tokyo Tanabe), a fortified minced bovine extract similar to Survanta; Alveofact (SF-RI1; Boehringer Co., Germany), a bovine surfactant from lung lavage; and Pneumactant (artificial lung expanding compound—ALEC; Britannia Pharmaceuticals), a synthetic surfactant of DPPC and PG in a 7:3 ratio. A synthetic, *complete* surfactant, Surfaxin (lucinactant or KL_4; Discovery Laboratories), composed of phospholipids and a synthetic analog of SP-B, has recently been developed and is undergoing clinical trials. The protein analog consists of a 21-amino acid chain of lysine and leucine in a 1:4 sequence.

Currently, for best distribution, the surfactants are given as a bolus liquid suspension in saline: Exosurf—5 ml/kg (67 mg DPPC); Survanta—4 ml/kg (100 mg phospholipids/kg); Infasurf—3 ml/kg (105 mg phospholipids/kg). The quantity of phospholipid given is approximately that normally present in the term newborn lung but 10 to 20 times that present in a premature infant with RDS. Exosurf, Infasurf, and Curosurf are given in two divided dose bolus aliquots and Survanta in four aliquots while turning the patient in different positions. In some infants, the initial instillation of such a large volume of fluid can cause some temporary instability and decreased oxygen saturations. However, the subsequent response to the surfactant can be remarkable. With establishment of an FRC and improved oxygenation, the inspired oxygen level can be quickly reduced. The degree of positive pressure ventilation can also be reduced with an improvement in compliance. However, this improvement is more likely to occur over several hours. The response to the protein-containing surfactants is more rapid than with the protein-free totally synthetic surfactant (Exosurf); clinical outcomes are similar except in the smallest infants where the protein-containing surfactant appears advantageous. Because of these factors, Survanta has evolved as the most common agent used, although the two newly approved protein-containing surfactants may alter the dominance.

In some infants, further weaning is not possible or symptoms worsen 6 to 12 hours after the initial treatment with surfactant. This may result from inadequate quantity or distribution of the initial dose or inactivation of the surfactant. Such infants treated with Exosurf or Curosurf should be retreated at 12 hours if their symptoms have persisted and they require greater than 40% oxygen on mechanical ventilation. Third or fourth treatments have been shown not to be more effective. Infants treated with Survanta or Infasurf are retreated within 6 to 12 hours, if necessary, with up to four (two of Infasurf) treatments in all, although few require the third and fourth doses. Although in general clinical use for 10 years, the optimal dose of these surfactants and the timing of repeat doses require further study. Exogenous surfactant treatment does not appear to inhibit the accelerated endogenous production of surfactant occurring in infants after a premature birth.

The use of surfactant has resulted in a major decrease in pulmonary-associated complications such as pneumothoraces and pulmonary interstitial emphysema to less than 10% and lessened time on mechanical ventilation. In early studies, a decrease was also seen in mortality, especially in the smallest infants and in cases of severe bronchopulmonary dysplasia. The incidence of severe intraventricular hemorrhage was not significantly changed in many studies, but the overall incidence has been decreasing over the last 10 years as a consequence of better perinatal and neonatal care of the extremely immature fetus or infant.

It is important that infants born prematurely at high risk for RDS be delivered at centers where adequate postnatal stabilization, mechanical ventilation, and neonatal intensive care can be provided. The cause of the prematurity (e.g., chorioamnionitis, abruptio placenta, placental insufficiency) can result in shock or coexistent sepsis and pneumonia. If indicated, the infant should receive volume expansion. If respiratory symptoms or other indications of infection are present, the infant should be given antibiotics after obtaining cultures; neonatal pneumonia can both mimic and coexist with RDS. Intervention with positive pressure, either by continuous positive airway pressure or intermittent mandatory ventilation, should be instituted early in the course of the RDS in infants requiring greater than 30% to 40% oxygen or in those who cannot maintain adequate ventilation because of small size and a combination of decreased lung compliance and increased chest wall compliance.

The advent of surfactant treatment adds another reason for early intervention. Although initial studies on surfactant treatment were done on a rescue basis of established disease in infants up to 1 day of age and following up to 12 hours of mechanical ventilation, later studies have indicated that the earlier the intervention, the shorter and more benign the course of the disease. It has been suggested that infants at high risk (<29 weeks' gestation or <1250 g in birth weight) receive *prophylactic* treatment in the delivery room, before the first breath. However, the resuscitation and stabilization of an infant can be complicated by treatment with surfactant. Moreover, because many infants in this weight range do not have RDS, prophylaxis results in overtreatment of infants who do not have RDS or may not require intubation. A compromise is prophylactic treatment of those infants at the greatest risk for mortality and morbidity (<27 weeks; <800 g) in the delivery room after initial resuscitation and ventilatory stabilization (usually first 5–10 minutes); other infants at high risk requiring intubation should be treated within the first half hour of life if they show evidence of RDS after initial stabilization.

In larger, more mature infants, surfactant treatment should be done within 1 hour after intubation for RDS (when infants have reached the requirements for mechanical ventilation). In infants who require 30% to 40% oxygen but whose symptoms are worsening, early intubation with surfactant treatment may result in extubation within 12 to 24 hours time. With the early institution of surfactant treatment, the initial use of noninvasive nasal continuous positive airway pressure as the primary treatment has actually decreased, which will continue as long as the delivery of the surfactant requires endotracheal intubation. Delivering exogenous surfactant by an aerosol is again being evaluated; however, the infant will probably need to be intubated for aerosol delivery to be effective. A novel approach, suggested by some Europeans, is intubation and surfactant treatment in the delivery room, followed by extubation and immediate nasal continuous positive airway pressure.

Infants with RDS frequently require mechanical ventilation. Most neonatal ventilators are pressure-limited, time-cycled, continuous flow ventilators. Initial treatment can be with rates of 20 to 60 breaths per minute, with inspiratory times of 0.3 to 0.5 second. Distending pressures vary with gestational age and clinical disease but range from 15 to 25 cm H_2O with 3 to 6 cm of positive end-expiratory pressure. Recently, neonatal ventilators have been modified to provide assist-mode or synchronous intermittent mandatory ventilation, allowing the infant to have less sedation and yet not fight the ventilator; use of such modes has further decreased length of mechanical ventilation.

After surfactant treatment, the attending physician must be ready to wean the ventilator parameters and inspired oxygen level. An infant with improved compliance on a pressure-limited ventilator will receive too large a tidal volume, which can result in severe air leaks. As with any mechanical ventilation in premature infants, bedside evaluation, indirect monitoring with transcutaneous oxygen and carbon dioxide monitors and saturation meters, and the availability of arterial blood gases with a rapid turnaround time are necessary for adequate care. Continuous tidal volume (flow) monitors having a low dead space may also be helpful.

High-frequency ventilation is available for use in neonates, but the routine use of high-frequency ventilators in the post-antenatal maternal steroid treatment and post-surfactant era has not been well studied. Earlier controlled trials on infants with RDS did not show any advantage of high-frequency ventilation over conventional ventilation, and did suggest that increased intraventricular hemorrhage and air leak occurred with the routine use of high-frequency ventilation. In infants who develop significant air leaks (e.g., bronchopulmonary fistula or pulmonary interstitial emphysema) or who are failing on conventional ventilation, high-frequency ventilation may be effective.

Infants with pneumonia, shock from sepsis or perinatal asphyxia, or any process that leads to pulmonary edema may not respond as well to surfactant treatment as infants with RDS alone, as these processes inhibit the surface tension-lowering properties of the surfactant given. More gestationally mature infants with such problems or when inadequately treated for RDS may develop so-called *persistent fetal circulation* or *persistent pulmonary hypertension of the newborn* and require other treatments. A rare complication of RDS is pulmonary hemorrhage, which is actually hemorrhagic pulmonary edema. This can be a life-threatening event when it does occur. Treatment with

high positive end-expiratory pressure, improvement of cardiac function, and intravascular volume expansion may be effective. When the infant is stabilized after the event, additional surfactant treatment may improve the situation. In some studies, the instillation of pulmonary surfactant (or physiologic instability with treatment) is associated with a slight increase of this otherwise low incidence (1% to 5%) phenomenon.

The use of pulmonary surfactant for other severe neonatal pulmonary problems is currently being studied. The indications include meconium aspiration syndrome, neonatal pneumonia, congenital diaphragmatic hernia, and pulmonary disease secondary to hyperventilation in the treatment of persistent fetal circulation. In each of these processes, a secondary relative surfactant deficiency can occur, which could be helped by the addition of surfactant. However, in such cases, caution and judgment must be used during treatment, as some marginally stable infants can have a marked and perhaps terminal deterioration with surfactant administration. A new experimental technique for treating meconium aspiration syndrome involves a large volume of pulmonary lavage with a dilute surfactant solution.

With improved techniques of mechanical ventilation and surfactant treatment, the mortality rate for RDS in larger infants is minimal with early intervention and treatment. A rare infant 35 weeks' gestation or greater who may not adequately respond to treatment and is failing conventional or high-frequency ventilation may be a candidate for extracorporeal membrane oxygenation (ECMO). The risk for intraventricular hemorrhage by 35 weeks' gestation is low enough that infants can tolerate the systemic heparinization necessary for this treatment. The treatment usually lasts 3 to 4 days, during which the underlying pulmonary process is allowed to heal. In larger infants who are candidates for ECMO and other infants too premature to be treated by ECMO but who fail treatment with an element of pulmonary hypertension, a clinical response may occur with a newly approved treatment with inhaled nitric oxide. Nitric oxide gas is a potent pulmonary vasodilator with minimal systemic effects. It is delivered in the inspiratory gas at concentrations of 1 to 40 parts/million. This treatment can reduce pulmonary vascular resistance sufficiently to improve gas exchange, allowing clinical stabilization and time for overall pulmonary improvement. Partial liquid ventilation with perfluorocarbons has been used in a limited number of infants as a rescue therapy.

Mortality in RDS is now limited primarily to those infants of 24 to 26 weeks' gestation (500–800 g birth weight), most of whom would have died in the presurfactant treatment era. This group also has a significant percentage of neurodevelopmental morbidity. In these infants, consideration is given to terminating treatment when significant central nervous system complications or severe pulmonary complications occur. Although the improvements in respiratory care and surfactant therapy have reduced the mortality of RDS, the basic problem of the premature infant is multisystem immaturity, which is the rate-limiting step in reducing mortality and morbidity. Also despite early and successful treatment of RDS, most develop a mild chronic lung disease with some oxygen dependency during much of the initial hospitalization. Long-term pulmonary effects at adult and geriatric ages are unknown.

An alternative to neonatal treatment is prevention of RDS by fetal treatment. The incidence and severity of RDS are reduced by maternal or fetal treatment with corticosteroids. When mothers are at risk for premature delivery, acceleration of fetal lung maturation can be achieved by the prenatal administration of maternal corticosteroids over a 2-day period. During this treatment, labor is inhibited to avoid delivery before the effect of the corticosteroids occurs. In addition to accelerating pulmonary maturation and reducing the risk and severity of RDS, the steroid therapy decreases the incidence of severe intraventricular hemorrhage in the premature infant. This latter effect is probably more important in decreasing the long-term morbidity now that surfactant is available for treatment of RDS. Another maternal treatment—thyroid-releasing hormone—has not been shown to add any benefit over maternal corticosteroid treatment combined with neonatal surfactant treatment.

Even with prevention of RDS by fetal therapy, no advantage is seen to a premature delivery. Optimally, the best treatment of RDS is prevention of prematurity. Understanding the cause and determining a treatment for premature labor are necessary for the ultimate cure of RDS.

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VIII. CHEST WALL AND NEUROMUSCULAR DISORDERS

74. DISORDERS OF THE THORACIC SPINE

Ann M. Romaker

Disorders that adversely affect the thoracic vertebral column can compromise respiratory function. The most common of these disorders are scoliosis, kyphosis, kyphoscoliosis, and ankylosing spondylitis.

Scoliosis is a lateral deviation of the spine; kyphosis is a posterior angulation. In scoliosis, the initiating curve is called the *primary curve*, and the *compensatory curve*, which restores postural balance, is called the secondary curve. The angle of the scoliosis, which is defined by the converging limbs of the curve, is expressed in degrees. The degree of kyphosis is defined by the angle between the upper limb of the spine and the vertical plane. Separately and in combination, scoliosis and kyphosis effect a number of changes on the thorax and its contents, resulting in gross distortion of thoracic configuration and volume. Even mild curves can affect lung function and work capacity. However, respiratory and cardiovascular compromise are noted most often when these deformities exist concomitantly (i.e., kyphoscoliosis).

The cause of kyphoscoliosis is unknown in approximately 80% of cases. In the remaining cases, the most common causes (in decreasing frequency) are neuromuscular disease (e.g., poliomyelitis, syringomyelia, neurofibromatosis), congenital defects of the spine, vertebral disease (e.g., tuberculosis, tumor, osteomalacia), and thoracic disease (e.g., emphysema, thoracoplasty). Idiopathic deformity is more common in female patients (4:1) and is usually not severe. In contrast, the deformity in poliomyelitis, tuberculosis, and congenital spine defects is often marked. Now that patients with cystic fibrosis are living into adulthood, an increased incidence of kyphosis secondary to osteoporosis is occurring. This osteoporosis is related to poor nutrition, use of corticosteroids, lower levels of sex steroids, and increased levels of circulating osteoclase-activating factors.

Clinical manifestations of severe kyphoscoliosis can include dyspnea, cyanosis, somnolence, and cor pulmonale. The severity of these findings reflects the degree of deformity. Clinical manifestations are unusual when kyphosis is less than 20 degrees and when scoliosis is less than 100 degrees; however, alterations in pulmonary function can be demonstrated with much milder disease (e.g., with lateral curves of 25 degrees).

Although the physiologic hallmarks of severe kyphoscoliosis are a gross reduction in lung volume and a small tidal volume, the ratio of tidal volume to vital capacity actually increases. To increase tidal volume further requires such a large increase in the work of breathing that these patients respond to a need for greater ventilation by increasing respiratory rate, not depth. Because anatomic dead space is fixed, such rapid, shallow ventilation results in a large amount of wasted (*dead-space*) ventilation per minute. Furthermore, anything that further reduces ventilation (e.g., sedatives, infection, obesity, asthma) can lead to marked reductions in alveolar ventilation, with consequent hypoxemia and hypercapnia.

Patients with severe thoracic deformity can live for many years without developing respiratory insufficiency. In fact, development of respiratory failure from a remediable cause does not imply a grim prognosis, as was once believed. Currently, median survival after a first bout of respiratory failure is 9 years. Although compression and kinking of pulmonary arteries can lead to some elevation of pulmonary vascular resistance, most cases of significant pulmonary hypertension are a consequence of alveolar hypoventilation. Evidence indicates that patients with kyphoscoliosis have a higher incidence of disordered breathing during sleep than normals, which may contribute to pulmonary vasoconstriction. If hypoventilation persists, cor pulmonale develops.

Individuals with severe thoracic deformity are at great risk of respiratory decompensation with minor insults such as viral or bacterial infections and sedation. Treatment is preventive and supportive in the adult. The primary objective is prevention with

appropriate immunizations, maintenance of good hydration, prompt attention to respiratory infection, and avoidance of sedatives. Supplementary oxygen may alleviate the vasoconstrictive element of pulmonary hypertension secondary to regional or global alveolar hypoventilation. Some patients can benefit from respiratory muscle training. Many others with persistent respiratory failure benefit from nocturnal mechanical ventilation. This increases lung compliance, decreases the work of breathing, and allows fatigued respiratory muscles to rest. It is now possible to provide positive pressure mechanical ventilation via face mask, alleviating the need for a tracheostomy in most patients. Both nasal continuous positive airway pressure masks and customized foam nosepieces have been used successfully. Negative pressure ventilators (e.g., cuirass, poncho) are also in use but are not generally tolerated by patients as well as the positive pressure types. Both, however, may allow even severely afflicted patients to remain at home.

Young patients in whom the spine is more flexible may benefit from internal fixation of the spine by a rod (Harrington rod); however, this benefit has not been consistently demonstrated. Adults gain no significant improvement in pulmonary function after corrective surgery. External corrections are considered less effective. Indications for surgery in young patients include (1) progression of disease despite good external brace care; (2) deformity that is too advanced to respond to external bracing; (3) scoliosis greater than 50 degrees; (4) intractable pain; (5) nonalignment of occiput over sacrum; and (6) psychiatric disturbances. However, both bracing and internal fixation can be associated with complications including further reductions in vital capacity. In many patients, however, disease progression is halted.

Ankylosing spondylitis is an uncommon arthritic condition that occurs predominately in men (4–8:1) aged 20 to 40 years. Approximately 90% of affected individuals have the histocompatibility antigen HLA-B27; 20% of those with HLA-B27 develop ankylosing spondylitis. In approximately one fifth of cases, peripheral joint manifestations are also present. Chest wall pain, usually pleuritic, is noted in more than 60% of patients. Thoracic spine involvement can result in fixation of the chest wall in an inspiratory position. Clinical manifestations, which can be insidious, include intermittent lower back pain, weight loss, anorexia, and fever; dyspnea is unusual. When dyspnea is present, it is more commonly caused by cardiac involvement than by pulmonary involvement. In a large Mayo Clinic study, the incidence of pleuropulmonary involvement was 1.35%. Severe respiratory symptoms are rare as long as diaphragmatic function is normal. Effective treatment for ankylosing spondylitis is not available; treatment in the early stages with steroids, immunosuppressive agents, or both has been proposed, but no data supporting their efficacy are available.

A distinctive upper lobe fibrobullous or fibrocavitary pulmonary process complicates a minority of cases of ankylosing spondylitis; its incidence has been reported to be between 1% and 30%. A marked male predominance is seen, far exceeding that of ankylosing spondylitis *per se*. The upper lobe changes usually develop many years after the initial skeletal manifestations. The cause is unknown. An unsatisfactory theory relates its pathogenesis to a vertical traction on the lung apices, caused by elongation of the thorax by diaphragmatic excursion in the face of a fixed, noncompliant chest wall. The peculiar apical and subapical location makes aspiration (caused by esophageal motility abnormalities) an unlikely reason for the process. The process bears no temporal relationship to axial radiotherapy (once commonly employed), as it lies outside the radiation ports and occurs in the absence of radiotherapy. Although no large-scale study is available, the process appears to occur equally in individuals with or without HLA-B27 positivity.

Several large surveys of patients with ankylosing spondylitis in Great Britain have suggested a twofold to threefold increased incidence of chronic tuberculosis; however, these surveys were based on death certificates or notification from tuberculosis registries and lacked bacteriologic confirmation. More recent studies have failed to substantiate an increased incidence of tuberculosis and suggest that early reports failed to recognize apical fibrocavitary disease as a sequela of ankylosing spondylitis.

Histologically, the initial manifestation of ankylosing spondylitis appears to be that of a nonspecific interstitial mononuclear cell infiltrate, associated with a variable

degree of fibroblastic proliferation and fibrosis. Advanced lesions show dense fibrosis, thin-walled bullae or cavities, and, at times, bronchiectasis. Apical pleural thickening is invariably present, and subapical pleural reactions have been described.

Clinically, patients may have a minimally productive cough and exertional dyspnea; these symptoms occur in patients with ankylosing spondylitis with chest wall restriction but no apparent pulmonary parenchymal abnormality. Hemoptysis is common but appears to be related to the presence of aspergillomas within the cavitary lesions. An increased incidence of spontaneous pneumothoraces has been reported.

Laboratory findings are nonspecific; a mildly elevated erythrocyte sedimentation rate and elevated levels of immunoglobulin A (IgA) have been described. Pulmonary function studies reveal a restrictive pattern (i.e., decreased static lung volumes and normal flows), again consistent with findings simply caused by chest wall restriction.

The chest roentgenogram initially shows a nodular or reticular pattern in the apical or subapical lung zones. This pattern tends to coarsen and become confluent, eventually appearing as dense consolidation. Upward retraction of hilar structures attests to upper lobe volume loss. Involvement may be initially unilateral, but most lesions progress to bilateral involvement. The apical lesions usually cavitate; in those appearing as dense fibrosis, tomography will often demonstrate otherwise inapparent cavities. Findings typical of aspergillomas are eventually present in one third to one half of all cavitary lesions.

The clinical course of ankylosing spondylitis is generally one of slow progression seen roentgenographically over months to years. In a few cases, extensive fibrosis eventually affected the upper one third of both lungs, but many tend to stabilize or apparently *burn out*. Symptoms from aspergillomas frequently dominate the clinical picture. Colonization of cavities with types I and III atypical mycobacteria has been reported.

Attempts at therapeutic intervention have not been systematically evaluated. Resection of the involved lung has been complicated by an unusually high incidence (50%) of bronchopleural fistulas and empyema, often sterile. Progressive involvement of remaining ipsilateral or contralateral lung is not infrequent. No drug has been identified that actually modifies the disease; however, nonsteroidal anti-inflammatory drugs, methotrexate, and sulfasalazine are frequently used.

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75. DIAPHRAGMATIC DISORDERS

David M. Burns

The diaphragm is the principal muscle of respiration during quiet breathing. Disorders of the diaphragm include paralysis, eventration, herniation, and diaphragmatic dysfunction; these events can be an important part of the pathophysiology of respiratory failure.

Paralysis is the most important clinical condition affecting the diaphragm. The paralysis can be unilateral or bilateral, and it can be transient or permanent. Each hemi-diaphragm is innervated by a phrenic nerve, originating with fibers from the third, fourth, and fifth cervical roots. Diaphragmatic paralysis can result from interruption or dysfunction of the phrenic nerve anywhere from its origins in the neck to the neuromuscular junction. Paralysis also can occur with disruption of the spinal cord at or above the level of the phrenic nerve roots. The most common causes of unilateral diaphragmatic paralysis are invasion by bronchogenic carcinoma, surgical section, thoracic trauma, and (presumed) postinflammatory neuropathy.

Bilateral diaphragmatic paralysis is usually the result of spinal cord trauma. Occasionally, idiopathic or postinfection neuropathy can present as bilateral paralysis, particularly when there has been preexisting unilateral diaphragmatic paralysis. Following cardiac surgery, certain patients may develop unilateral or bilateral diaphragmatic paralysis. This paralysis is probably the result of a thermal injury to one or both phrenic nerves caused during cooling of the heart, although intraoperative trauma to the nerve also can cause phrenic paralysis. Better intraoperative cooling techniques have made this phenomenon less common.

Patients with unilateral diaphragmatic paralysis are usually asymptomatic, whereas those with bilateral diaphragmatic paralysis usually experience orthopnea and dyspnea with exertion. With diaphragmatic paralysis, the intercostal and the accessory muscles become the chief muscles of inspiration. Orthopnea occurs when these patients are supine because the abdominal contents push on the flaccid diaphragm, elevating the rib cage. The increase in supine rib cage volume severely compromises the ability of the intercostal and accessory muscles to generate an inspiratory volume. On physical examination, patients with bilateral diaphragmatic paralysis often show prominent activity of the accessory muscles of inspiration (i.e., intercostals, scalene, and sternocleidomastoids), because their inspiration results primarily from elevation of the rib cage by these muscles. Patients often favor the upright position, from which they can fixate their pectoral girdle and use their pectoral muscles to elevate the chest wall and breathe more efficiently. When supine, they display a classic paradoxic inward motion of their anterior abdominal wall during quiet inspiration.

Pulmonary function testing in diaphragmatic paralysis reveals a reduced total lung capacity, vital capacity, inspiratory capacity, and maximal inspiratory pressure. Unilateral paralysis reduces total lung capacity and maximal inspiratory pressure by 20% to 25%. A low inspiratory capacity that falls still further in the supine position suggests diaphragmatic paralysis.

The definitive diagnosis of diaphragmatic paralysis has traditionally rested on fluoroscopic demonstration of diminished, absent, or paradoxic upward motion during normal inspiration. The *sniff* maneuver is used to enhance this paradoxic upward movement during a quick inspiration; however, fluoroscopy can fail to identify bilateral diaphragmatic paralysis in patients who have learned to breathe by actively expiring below functional residual capacity with forceful contraction of their abdominal muscles. Such a maneuver displaces the flaccid diaphragm upward and compresses the thoracic cavity, thus allowing the elastic recoil of the rib cage and the weight of the abdominal contents to passively assist with the subsequent inspiration. Fluoroscopically, this passive downward motion of the diaphragm is easily misinterpreted as an active contraction. Diaphragmatic performance is more reliably assessed with fluoroscopy by performing a maximum inspiratory maneuver from functional residual capacity against a closed airway. The normal diaphragm will move slightly downward, but the paralyzed

diaphragm will move paradoxically upward. A more comprehensive evaluation can be made by recording gastric and esophageal pressures together with rib cage and abdominal motions. The pressure across the diaphragm (Pdi) can be estimated by the difference between gastric and esophageal pressures. Pdi should increase with inspiration and with a maximal inspiratory pressure maneuver, and the abdomen should move outward. The failure to increase Pdi or the generation of a Pdi by inward motion of the abdomen suggests diaphragmatic paralysis. The functional integrity of the phrenic nerves can also be assessed by electromyography.

The therapy and prognosis of diaphragmatic paralysis relate to the underlying disorder. When interruption of the neural control of the diaphragm has occurred centrally, leaving the phrenic nerve intact, considerable improvement in pulmonary status can be achieved by electronic pacing. Electrodes are surgically implanted around the phrenic nerve, and electronic signals are generated using an external radiowave source worn by the patient. Following installation of such a device, weeks or months may be required to achieve full effect if diaphragmatic atrophy has antedated pacing. Patients with bilateral diaphragmatic paralysis are usually paced using one side at a time, as this maintains adequate alveolar ventilation and prevents diaphragmatic fatigue. Patients whose paralysis is postviral or postcardiac surgery often recover function, but this recovery can take 2 to 6 months.

Diaphragmatic fatigue is a common clinical problem in patients requiring mechanical ventilation. It occurs when the energy expenditure of the diaphragm exceeds the capacity of the blood supply to provide oxygen and nutrients. An increase in the fraction of the maximal contractile pressure developed by the diaphragm during a breath and the fraction of ventilatory time spent in inspiration (i.e., with the diaphragm contracting) both independently increase the likelihood of diaphragmatic fatigue. The multiple of these two fractions, which is called the *tension time index*, predicts the development of fatigue when a value of 0.15 is exceeded. The blood flow to the diaphragm is also an important determinant of fatigue. The threshold for fatigue is reduced under hypotensive or hypoxemic conditions.

Muscle rest is the primary therapy for respiratory muscle fatigue; however, a number of agents, most notably aminophylline, increase diaphragmatic contractility and endurance in the experimental setting. The significance of these findings for therapy of clinical respiratory muscle fatigue remains uncertain, but the complications of these agents probably outweigh their clinical utility in patients with respiratory muscle fatigue.

Eventration of the diaphragm is a rare congenital malformation consisting of failure of muscular development of all or part of the diaphragm. It is more common in men. Complete eventration is almost always left-sided, whereas partial eventration is more common on the right. The term *eventration* has become synonymous with long-standing elevation of the diaphragm from any cause, although strictly speaking the term should be reserved for the congenital malformation. On chest roentgenogram, eventration is apt to be confused with a diaphragmatic hernia or pleuropericardial cyst. In the adult, the abnormality is frequently discovered as an incidental roentgenographic finding. Individuals are usually asymptomatic; however, with obesity considerable respiratory compromise may be noted. In neonates, involvement of an entire hemidiaphragm can lead to severe respiratory and cardiac compromise from thoracic compression by displaced abdominal contents. This constitutes a surgical emergency.

Herniation of abdominal contents through the diaphragm can occur through regions of congenital defect or weakness, including the esophageal hiatus, the posterolateral or pleuroperitoneal foramen of Bochdalek (in infants), and the retrosternal (parasternal) foramen of Morgagni (any age). Hiatal hernia (via the esophageal hiatus) is relatively common in the adult. It is usually asymptomatic but can cause retrosternal burning and pain, which are aggravated by lying flat and relieved by antacids. Occasionally, hiatal hernia can be associated with nocturnal aspiration and recurrent pneumonia.

Herniation through the posterolateral aspect of the diaphragm (foramen of Bochdalek) is the most common and serious hernia in infants. It usually presents as an acute respiratory emergency at or shortly after birth and requires immediate surgical repair.

Herniation through the foramen of Morgagni is more common in adults and is often asymptomatic. Obesity is an important predisposing factor. On chest roentgenogram, the abnormal shadow appears retrosternally, usually along the right sternal border, and can mimic a pericardial cyst.

Tears or rupture of the diaphragm can occur with blunt or penetrating trauma. Use of single-point, lap-belt restraint systems in high-speed motor vehicle accidents is associated with diaphragmatic rupture. Although trauma statistics support an increase in the frequency of right-sided rupture, this injury usually occurs on the left. Herniation of the abdominal contents can cause respiratory distress and substernal pain. This injury can be missed in the unconscious trauma victim until an upright chest roentgenogram shows absence of the affected diaphragmatic outline.

The most common functional disorder of the diaphragm is the mechanical disadvantage that results from an extreme degree of hyperinflation with severe airways obstruction or advanced emphysema. During the course of chronic obstructive pulmonary disease (COPD), the diaphragm is displaced inferiorly and is flattened out, thereby reducing the pressure that can be generated as the diaphragm contracts. Some adaptation of the diaphragm occurs with emphysematous change to make the diaphragm more fatigue resistant, but mechanical disadvantage is more important than fatigue in causing ventilatory limitation. Lung volume reduction surgery can reduce lung volume in selected patients, restoring mechanical advantage to the diaphragm and improving exercise tolerance.

Other functional diaphragmatic disorders include hiccup (singultus) and diaphragmatic flutter. Hiccup is usually a benign disorder that results from repetitive, abrupt inspiratory spasm of the diaphragm, with associated closure of the glottis. It commonly follows transient diaphragmatic irritation, such as occurs with gastric distention caused by aerophagia or overeating, and treatment of acute gastritis can be an effective means of reducing the frequency of hiccups. Protracted episodes may follow upper abdominal surgery, cardiac surgery, or inferior myocardial infarction. Hiccup can also be associated with mediastinitis, tumor invasion, pericarditis, pleuritis, gastritis, and peritonitis. In patients with cardiac pacemakers, hiccup can signal perforation of the right ventricle by the pacing electrode. Diaphragmatic flutter (respiratory myoclonus or Leeuwenhoek's disease) is a rare disorder characterized by dyspnea associated with frequent diaphragmatic contractions (~100/min) superimposed on the normal respiratory excursion and by prominent epigastric pulsations. The attacks are paroxysmal. Diphenylhydantoin may be helpful.

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76. NEUROMUSCULAR DISEASES AND SPINAL CORD INJURY

David M. Burns

A variety of neuromuscular and spinal cord diseases can adversely affect the respiratory system, ultimately leading to ventilatory insufficiency and, possibly, death. Such conditions include skeletal muscle disorders (the muscular dystrophies, polymyositis, and myotonic dystrophy); peripheral nerve disorders (polyneuritis); neuromuscular junction disorders (myasthenia gravis, botulism, and the Eaton–Lambert syndrome); and spinal cord disorders (amyotrophic lateral sclerosis, Guillain–Barré and spinal cord injuries). The pathophysiology of these disorders involves dysfunction of the chest wall. The lung itself is not directly affected unless aspiration, atelectasis, or pneumonia has complicated the illness.

The chest wall is composed of three interdependent components: the rib cage, the diaphragm, and the abdomen. Inspiration can be accomplished by elevation of the rib

cage or by downward displacement of the abdominal contents. Although the intercostal and accessory muscles of inspiration can assist inspiration, the diaphragm is the major active muscle used in quiet breathing. As the diaphragm contracts and shortens, an obligatory movement of the rib cage and abdominal contents is determined by the relative compliance of these two components. For example, stiffening of the abdomen by contraction (or spasticity) of the abdominal muscles results in more rib cage elevation and less abdominal displacement for any given diaphragmatic shortening. Expiration to functional residual capacity (FRC) is usually passive, but the intercostal and abdominal muscles can assist it. Expiration below FRC is accomplished predominantly by the abdominal muscles. A neuromuscular disease can have an impact on the chest wall by producing a generalized loss of muscle strength or by weakening selective muscle groups.

Diseases that usually cause a generalized loss of respiratory muscle strength include skeletal muscle disorders, neuromuscular junction disorders, some peripheral nerve disorders, and myasthenia gravis. Inspiratory and expiratory lung volumes are reduced, whereas FRC remains normal. The most sensitive tests of respiratory muscle weakness are static maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). To perform these tests, the patient is encouraged to inspire or expire with maximal effort against an occluded external airway from residual volume (MIP) or from total lung capacity (MEP). The pressures are easily recorded using a manometer. The MIP and MEP can be abnormal early in the course of disease, even when the static lung volumes are normal. These pressures, along with the vital capacity (VC), are simple, reproducible measurements obtainable at bedside and useful in following the course of an illness and in evaluating ventilatory reserve or drug therapy. A MIP of 30 cm H_2O or less and a VC of 800 ml or less have been widely used as indicators of impending ventilatory failure. Arterial blood gases are less reliable predictors, because patients often maintain normal $Paco_2$ until their ventilatory limitation begins to encroach on the tidal volume. The limitations of blood gases and periodic recording of the VC in predicting acute respiratory failure in patients with neuromuscular disease suggest that early admission to an environment where intensive monitoring is possible is advisable when the disease process is unstable.

Many patients with these disorders have underlying obstructive lung disease or, in the case of myasthenia gravis, are receiving anticholinesterase therapy, which can increase airways resistance. Expiratory flow obstruction not only increases the work of breathing but also increases the FRC. Because the MIP decreases with increasing lung volume, an increased FRC can result in a drop in the ability to inspire and precipitate ventilatory failure. If flow obstruction is present, the addition of a β_2-sympathomimetic, aminophylline, and good pulmonary toilet may reverse the changes in airways resistance and increase both MIP and VC.

Diseases that selectively weaken respiratory muscle groups include high spinal cord injuries and amyotrophic lateral sclerosis. Acute spinal cord injuries are the most clearly understood examples of this impairment. Lesions below L1 rarely cause ventilatory insufficiency. Lesions between T5 and L1 compromise the abdominal muscles and limit the ability to expire. Complete paralysis of the abdominal muscles results in almost complete loss of the capacity to expire below FRC. Lesions in the thoracic spine paralyze the external and internal intercostal muscles and further compromise the ability to forcefully expire. These lesions also limit the inspiratory capacity. If the cord lesion is in the cervical region below C5, the only remaining muscles of respiration are the diaphragm and accessory muscles. The VC can be reduced to 30% to 40% of the predicted value and expiration will be entirely passive. If the patient is studied in the upright position, rather than supine, an additional loss in VC will occur because of the reduced end-expiratory length of the diaphragm in the upright position. This decreased length results in a reduction of the tension developed by the diaphragm for a given neural stimulus, as well as a reduction in the volume displaced by the diaphragm before flattening destroys its mechanical advantage. Both of these phenomena result in a drop in the VC. Cord lesions in the C3 to C5 region can partially or totally denervate the diaphragm. Consequently, a loss may occur in the ability to maintain adequate, spontaneous ventilation. The accessory muscles alone are able to maintain a tidal volume of 50 to 100 ml in the acute phase of the injury, but this volume is hardly compatible with life.

The evaluation of respiratory muscle function after a spinal cord injury should include measurements of static and dynamic lung volumes, as well as the MIP and MEP. Measurements taken shortly after an injury will be the lowest. Even without neurologic improvement, increases in the ventilatory capacity will occur because of adaptations by the respiratory muscles. Improved strength of the remaining musculature accounts for part of that increase, and inspiratory muscle training can improve the exercise endurance of these patients. Quadriplegic patients studied several years after injury can move as much as 600 ml of air using only their accessory muscles. Another mechanism of adaptation is the development of abdominal and intercostal muscles spasticity. This spasticity decreases the paradoxic inward motion of the rib cage with inspiration and stiffens the abdomen, resulting in more rib cage motion for any given degree of diaphragmatic shortening. These changes may return the VC to 60% to 70% of the predicted value in cervical cord lesions and to almost normal in thoracic lesions. A final ventilatory adaptation is an increase in the end-expiratory point, probably in response to the loss of expiratory capacity. At end expiration, patients maintain some inspiratory tone, producing a higher lung volume, which enables them to redevelop the ability to breathe out below FRC.

Patients with amyotrophic lateral sclerosis develop progressive weakness of focal muscle groups. Classically, this disease involves the cervical cord and spares the mid and lower thoracic cord. Thus, diaphragmatic function is affected, whereas intercostal and accessory muscles are spared. Patients' diaphragms appear high on chest radiographs and they ventilate predominantly with their intercostal and accessory muscles. Unlike patients with cervical cord lesions and functioning diaphragms, patients with amyotrophic lateral sclerosis show no loss and sometimes a gain in VC, measured in the upright rather than the supine position. The loss of anterior horn cells is progressive, and the natural course of the disease is a progressive loss of VC and a reduction in the MIP and MEP until ventilatory failure supervenes.

In patients with a severe limitation of ventilatory reserve because of either muscle weakness or spinal cord disease, the VC should be measured in all positions that the patient can assume. Thus, any additional position-induced loss of ventilatory capacity can be avoided.

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During exercise, early signs of diaphragm fatigue were present in 7 of 10 complete cervical cord injury patients and in 4 of 5 patients with prior poliomyelitis infection requiring chronic treatment with intermittent positive pressure ventilation at night, as indicated by a reduction in central frequency of the diaphragm electromyogram power spectrum and an increase in the diaphragmatic tension-time index.

26. Shatney CH, Brunner RD, Nguyen TQ. The safety of orotracheal intubation in patients with unstable cervical spine fracture or high spinal cord injury. *Am J Surg* 1995;170:676; discussion 679.

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Nine individuals with tetraplegia (between C3 and C7) performed a target flow endurance training of the inspiratory muscles, twice a day for 15 minutes. Training had no effect on the inspiratory VC, forced inspiratory pressure in 1 second, forced expiratory pressure in 1 second, and maximum inspiratory pressure; however, training enhanced the endurance capacity of the inspiratory muscles with a concomitant increase in the aerobic exercise performance.

28. McDonald CM, et al. Profiles of neuromuscular diseases. *Am J Phys Med Rehabil* 1995;74(Suppl):S93.

A set of clinical series reviewing neuromuscular diseases including Becker's muscular dystrophy, myotonic dystrophy, limb-girdle syndromes, hereditary motor and sensory neuropathy, types I and II; and spinal muscular atrophy.

29. Wright NC, et al. Aerobic walking in slowly progressive neuromuscular disease: effect of a 12-week program. *Arch Phys Med Rehabil* 1996;77:64.

Moderate-intensity aerobic exercise training is well tolerated and may provide modest improvement in aerobic capacity in patients with slowly progressive neuromuscular disease.

77. SLEEP APNEA, ALVEOLAR HYPOVENTILATION, AND OBESITY-HYPOVENTILATION

José S. Loredo

The spectrum of sleep-disordered breathing ranges from intermittent snoring, which is primarily a nuisance and has no significant health sequelae, to the obesity-hypoventilation syndrome, which is associated with severe morbidity and high mortality. In between these two conditions are disorders of gradually increasing impact on morbidity and mortality including chronic snoring, upper airway resistance syndrome, and sleep apnea.

Obstructive sleep apnea syndrome is characterized by repetitive upper airway obstruction during sleep, often resulting in arousals from sleep and hypoxemia. The most common presenting symptoms are excessive daytime somnolence and loud snoring. A syndrome of intermittent nocturnal upper airway obstruction in *pickwickian* patients with obesity, hypersomnia, and obstructive sleep apnea was described in 1965 and thought to be a rare condition, mainly associated with morbid obesity. However, recent data indicate that the prevalence of sleep apnea syndrome in middle-aged working men and women is 4% and 2%, respectively. Obstructive sleep apnea is the most

common dyssomnia recorded in sleep disorders clinics in the United States. The cause of obstructive sleep apnea is not well understood. However, a narrowed upper airway, loss of upper airway motor tone during sleep, and decreased drive to breathe have been implicated in the pathophysiology. Strong epidemiologic and experimental data link obstructive sleep apnea with the development of systemic hypertension and other cardiovascular complications. The mechanism for this association is unclear, but chronic intermittent hypoxemia and frequent arousals leading to hyperactivity of chemoreceptors and the sympathetic nervous system may be involved.

Three basic types of sleep disordered breathing exist: (1) apnea, cessation of airflow for 10 seconds or more; (2) hypopnea, 50% or greater decrease in airflow for 10 seconds or longer, associated with either arousal or oxyhemoglobin desaturation: and (3) respiratory effort-related arousals—the upper airway resistance syndrome (UARS).

Three types of apnea have been described: (1) obstructive apnea, in which oronasal airflow is blocked and diaphragmatic efforts continue; (2) central apnea, in which diaphragmatic and intercostal efforts cease; and (3) mixed apnea, an obstructive apnea with an initial central component. Evidence of full or partial upper airway obstruction (hypopneas, UARS, obstructive or mixed apnea) is present in most symptomatic patients with sleep apnea. Collected series of patients presenting with the typical picture of hypersomnia and sleep apnea have demonstrated the following distribution of apneic episodes: (1) obstructive and mixed, 85% to 90%; and (2) central, 10% to 15%. Both children and adults may be affected; however, the incidence of obstructive apnea and mixed apnea is highest in middle-aged men. The syndromes of obstructive and mixed sleep apnea are clinically similar and, therefore, are grouped together. UARS differs in that oxyhemoglobin desaturation and obvious apneas or hypopneas are not evident in the standard polysomnogram. Excessive daytime sleepiness is the most common presenting symptom, which may reflect the numerous arousals during sleep (often occurring hundreds of times per night) that result in severe sleep fragmentation. The bed partner often notes loud snoring, choking spells, abnormal motor activity during sleep, and periods of apnea. Changes in personality, cognitive impairment, and male sexual dysfunction can lead to family and employment discord. These patients also have higher rates of automobile accidents than normals.

On physical examination, 70% of the sleep apnea patients have truncal obesity. It is not unusual to find them snoring in the waiting room. Hypertrophy of the tonsils and adenoids appears to be the cause of the upper airway obstruction in children. Malformations of the jaw and maxilla (e.g., retrognathia, micrognathia, and narrow high arching palate) are noted occasionally. More commonly, the adult sleep apnea patient presents with an erythematosus, enlarged and edematous uvula, prominent tonsillar pillars, and drapelike soft palate, reducing the caliber of the oropharyngeal opening. In some patients, however, the physical examination can be entirely normal. Despite having a narrow oropharyngeal opening, airway obstruction during the waking state is usually absent secondary to neuromuscular compensation. During sleep, this neuromuscular compensation is lost, predisposing to upper airway obstruction. In the awake state, pulmonary function tests, arterial blood gases, and ventilatory response to carbon dioxide are usually normal, unless the separate effects of morbid obesity or another disease are present. Systemic hypertension is present in up to 50% of patients. Pulmonary hypertension and erythrocytosis can occur in severe cases, although this is more often associated with chronic hypoxemia.

The diagnosis of the sleep apnea syndromes can be made most accurately by documenting apneic episodes with polysomnographic monitoring of sleep stages (i.e., electroencephalogram, oculogram), oronasal airflow, ventilatory effort (esophageal pressure or chest wall motion), heart rate, and arterial oxygen saturation. To be considered significant, apneic episodes must last longer than 10 seconds and occur repetitively. The Apnea/Hypopnea index (AHI), also known as the Respiratory Disturbance index (RDI), is used to determine the severity of sleep apnea. These represent the number of apneas plus hypopneas per hour of sleep. An AHI less than 5 is considered normal, whereas an AHI more than 30 is considered severe.

The pathophysiology and hemodynamic consequences of the sleep apnea syndromes have been studied extensively. During an obstructive episode, the posterior wall of the hypopharynx collapses and the strap muscles of the neck become hypotonic as

documented by electromyographic recordings. As the apneic episode continues, hypercapnia and hypoxemia develop. Progressive increases in negative intrathoracic pressure develop with the increasing efforts to breathe against the obstruction. Systemic and pulmonary hypertension, sinus bradycardia, and a variety of arrhythmias and conduction disturbances can occur. A loud snort may signal the end of the obstruction, which correlates with an electroencephalogram pattern of arousal from sleep. Subsequently, abnormalities of gas exchange and hemodynamics resolve rapidly, unless repetitive apneic episodes occur, a frequent situation in severely affected individuals.

Treatment of the obstructive sleep apnea patients should always include behavioral interventions: weight reduction; avoidance of alcohol, sedatives, sleep deprivation, and the supine sleep position; and smoking cessation. Weight reduction to optimal levels can be curative in some cases. However, even modest weight reductions can result in significant reductions in sleep apnea severity.

Pharmacologic therapy for sleep apnea has been disappointing. Nocturnal nasal oxygen therapy can improve arterial oxygen saturation, but it does not significantly change the AHI. Continuous positive airway pressure (CPAP) has become the preferred method of treatment for sleep apnea. CPAP maintains upper airway patency during sleep by creating a pneumatic splint. It can effectively control sleep apnea and arousals and reverse oxygen desaturation in most cases. However, only about one half of patients are compliant with CPAP and use it regularly. For this reason, oral appliances, although not as effective as CPAP, have become more popular in patients with mild to moderate sleep apnea. The most effective oral appliances are those that advance the jaw, enlarging the upper airway, and are adjustable. Surgical procedures that increase upper airway size (e.g., uvulopalatopharyngoplasty) can effectively eliminate snoring, but frequently fail to control sleep apnea adequately, especially when the sleep apnea is more severe. Unfortunately, no method can predict which patients will benefit from surgical treatment. Tracheostomy, a last resort that is rarely applied, is consistently effective in relieving signs and symptoms of obstructive sleep apnea. Finally, surgery to advance the mandible and elevate the hyoid bone has been successful in selected centers. An effort should be made to identify treatable conditions that may be associated with sleep apnea (e.g., hypothyroidism, use of testosterone). In children, removing obstructing tonsils and adenoids is usually curative.

Pure central sleep apnea is often associated with the older age, central nervous system disorders, congestive heart failure, and sleeping at high altitude. It can be associated with high sensitivity to carbon dioxide and conditions that promote hypocapnia. Oral acetazolamide and nasal CPAP have both been successful in treating patients with central sleep apnea. Supplemental oxygen can also be beneficial, especially in central sleep apnea associated with high altitude.

Alveolar hypoventilation is defined as an elevation in the arterial P_{CO_2} more than 45 mm Hg because of a reduction in minute ventilation. The rise in alveolar P_{CO_2} will lead to a decrease in alveolar P_{O_2} and result in hypoxemia. Alveolar hypoventilation can occur with a number of disorders, referred to as the *hypoventilation syndromes*. Although hypercapnia and hypoxemia can be evident during wakefulness, these are usually more severe during deep sleep in most cases.

The syndrome of primary alveolar hypoventilation (Ondine's curse) is a rare disorder characterized by hypercapnia and hypoxemia that develops mostly in young adult males without abnormalities of the lung parenchyma, chest wall, respiratory muscle function, or voluntary control of ventilation. *Central alveolar hypoventilation* is a term used for those patients whose alveolar hypoventilation is caused by an identified central nervous system process such as destructive lesions in the medullary chemoreceptor. Congenital central hypoventilation is a very rare disorder of ventilation control (<100 cases described in the English literature) diagnosed in early childhood that may have a familial component. In all cases of primary alveolar hypoventilation, the central autonomic regulation of ventilation fails, resulting in an inability to integrate the neural input from peripheral chemoreceptors.

The clinical manifestations include lethargy, somnolence, and morning headaches. Dyspnea is remarkably absent unless congestive heart failure supervenes. Apnea during sleep is often prominent. Cyanosis with a normal alveolar-arterial O_2 gradient, which is the most common physical finding, can usually be reversed by voluntary

hyperventilation. Polycythemia and cor pulmonale are present in 50% of cases. Although hypercapnia and hypoxemia at rest are noted in the vast majority, arterial blood gases occasionally are normal, and an unexplained metabolic alkalosis may be a clue to previous chronic hypercapnia. Pulmonary function testing reveals normal lung volumes and flow rates; however, ventilatory response to carbon dioxide inhalation is greatly diminished or absent. The response to hypoxia is frequently impaired as well. Breath-holding time is often prolonged, and exercise may result in worsening of hypoxemia and hypercapnia because of impaired chemoreceptor response.

Several forms of therapy have been proposed. Respiratory stimulants are generally ineffective. Rocking beds or mechanical ventilatory assistance (bilevel positive airway pressure via a nasal mask) have been useful in severe cases, particularly at night when the hypoventilation is most severe. Nocturnal phrenic nerve pacing has been described as safe and effective and may be the treatment of choice in severely affected individuals.

The obesity-hypoventilation syndromes are composed of a group of disorders with diverse causes and pathogenetic mechanisms relating obesity and alveolar hypoventilation. They were originally lumped together as the *pickwickian syndrome* by Burwell and Robin, named after a character in Dickens's *Pickwick Papers* (*the fat boy Joe*) who was obese and continually falling asleep.

Studies of the cause of the obesity-hypoventilation syndrome have demonstrated that hypoventilation is not caused by simple obesity and probably results from an imbalance between ventilatory drive and ventilatory load. The decreased ventilatory drive is inherited in some subjects and acquired in others. The increased ventilatory loads inhibiting ventilation and gas exchange in these patients include (1) obesity with its increased work of breathing and interference with the mechanical efficiency of ventilation; (2) heart failure; (3) diffuse airway obstruction; and (4) recurrent apneas and blood gas derangements of obstructive sleep apnea. The obesity hypoventilation syndrome patient is at a high risk of in-hospital mortality and morbidity, often experiencing sudden unexpected death.

The findings on history and physical examination define this syndrome. Patients are severely hypersomnolent and fall asleep at the most inappropriate times. Although snoring is not a universal finding, these patients often have a long history of loud and disruptive snoring. On physical examination, patients are obese, often more than 50% above their ideal weight. They may have a ruddy complexion and cyanosis caused by hypoxemia and secondary erythrocytosis. They often have a short, thick neck, an enlarged uvula, and a small oropharyngeal opening. They may have crackles or wheezes on chest examination and demonstrate hepatomegaly, peripheral edema, and other findings of right ventricular failure.

Chest films show an enlarged heart and small lung fields with pulmonary congestion. Electrocardiograms often demonstrate right atrial and ventricular enlargement. Arterial blood gases demonstrate hypoxemia and hypercapnia, with a widened alveolar-arterial oxygen gradient. However, these patients can voluntarily hyperventilate and normalize their P_{CO_2}. Approximately one half of these patients have erythrocytosis. Spirometry demonstrates a lower than normal forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), with some patients having evidence of superimposed airway obstruction (i.e., FEV_1/FVC of <75%). The total lung capacity is approximately 20% smaller and the maximal voluntary ventilation 40% lower than that of patients with simple obesity. Tests of ventilatory control show a diminished response to both hypercapnia and hypoxemia. Polysomnography demonstrates moderate to severe obstructive sleep apnea, often with prolonged and severe hypoxemia, in an overwhelming majority of these patients. A minority of patients with obesity-hypoventilation syndrome demonstrates few, if any, apneas on full-night sleep studies.

Clinical evaluation of these patients should include a careful history and complete physical examination, arterial blood gases, spirometry, maximal inspiratory and expiratory pressures, thyroid function tests, and overnight polysomnography. This evaluation should focus on any condition that could contribute to persistent daytime hypoventilation such as hypothyroidism, severe obstructive sleep apnea, or respiratory muscle weakness. In addition, in this evaluation, consider other sources of ventilatory impairment, such as left ventricular failure and diffuse airway disease.

These patients should be thoroughly evaluated and treated to avoid serious complications, which include acute ventilatory decompensation with mechanical ventilation and sudden death. Therapy should focus on reducing ventilatory loads and increasing ventilatory drive. Several studies have suggested that progestational ventilatory stimulants can improve daytime ventilation and oxygenation in patients with sleep apnea. The occurrence of male sexual impotency in many of these patients and the concern that these drugs may increase the risks of cardiovascular or thromboembolic disease limit their use. The risk of deep venous thrombosis and pulmonary embolism is great in these obese, inactive patients. Sedatives, alcohol, and other ventilatory depressants should be avoided. Nocturnal and daytime oxygen supplementation must be used with caution to avoid further ventilatory depression and worsening hypercapnia. An aggressive weight loss program should be instituted. Weight loss decreases the work of breathing, increases vital capacity, and increases ventilatory drive in these patients. A reduction of body weight of 20 to 40 kg has normalized P_{CO_2} in some patients with the pickwickian syndrome. Unfortunately, permanent weight loss in these patients is a difficult matter, and may require long-term in-hospital treatment or bariatric surgical. Nocturnal nasal bilevel positive airway pressure should be instituted to correct nocturnal hypoventilation. It should also be carefully titrated to abolish obstructive apneas. CPAP has been shown to improve cases of left ventricular failure and daytime ventilation.

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IX. ENVIRONMENTAL AND OCCUPATIONAL DISEASES

78. APPROACHES TO OCCUPATIONAL-ENVIRONMENTAL LUNG DISEASE

William G. Hughson

The term *occupational-environmental lung disease* (OELD) describes a diverse group of conditions that are caused or aggravated by exposures in the workplace or environment; Table 78.1 lists some examples. Correct assessment of OELD requires systematic collection of data from multiple sources. Table 78.2 outlines the general approach to these patients, which begins with a careful review of the symptoms, with special emphasis on their relationship to patient activities. It is important to determine whether symptoms are worse at work and improve when away on weekends or holidays. Cigarette smoking and pre-existing conditions such as asthma or allergies must be recorded. Nonrespiratory causes of dyspnea, including obesity or cardiac disease, should be evaluated as part of the general medical history.

A unique aspect of OELD is the crucial importance of the occupational-environmental history (Table 78.3); failure to reach a correct diagnosis usually begins with insufficient attention to collecting and evaluating this information. It is essential to obtain a complete chronology of all jobs held by the patient. Many conditions (e.g., asbestosis) have a long latency between exposure and disease; enquiries limited to the current occupation may fail to identify the culpable exposures.

After completing the history, a workplace or environmental cause may be suggested. Data are then collected to narrow the differential diagnosis. The physical examination should seek not only respiratory signs but also nonpulmonary causes of dyspnea such as heart disease and obesity. Chest radiographs are always important and can be central to the diagnosis of certain conditions (e.g., silicosis). However, the radiographs may be normal (e.g., occupational asthma) or the findings nonspecific. For example, cigarette smoking increases the profusion of irregular densities in the parenchyma, confounding the diagnosis of asbestosis. Confusion can be avoided if the radiologist is a National Institute for Occupational Safety and Health-certified B reader experienced in OELD. Pulmonary function tests are used to determine the general pattern (e.g., restrictive or obstructive) and degree of impairment. Exercise testing is often included to assess work capacity. Bronchial hyperreactivity can be identified using nonspecific agents (e.g., methacholine or histamine) or specific agents from the workplace. Special studies (e.g., skin tests, radioallergosorbent test assays) can be useful in identifying sensitization to workplace or environmental antigens. Invasive techniques (e.g., bronchoscopy, bronchoalveolar lavage, and open lung biopsy) may be necessary in selected cases.

After data have been collected from the patient, the focus then shifts to the workplace and environment. Industrial hygiene information can be obtained from the employer. This includes material safety data sheets for all agents used by the patient. The employer is legally obligated to provide these safety data sheets, which describe chemical constituents and toxicity. In some cases, they can be supplemented with air testing data or results of previous inspections by government agencies. Often, the workers' compensation insurance company will have information, including health effects in other workers. When possible, a site visit to the workplace can provide first-hand observation of workplace practices, ventilation, and personal protective equipment. Recommendations may then be made for additional air quality or other industrial hygiene testing. After exhausting all these sources, it is frequently necessary to perform a literature review concerning specific exposures and their known health effects. Consultation with experts such as industrial hygienists and toxicologists may be required.

Table 78.1. Examples of occupational-environmental lung disease

Disorder	General agent	Examples
Industrial bronchitis	Irritants	Gases, smoke, fumes
Occupational asthma	Chemicals	Isocyanates
	Animal protein	Laboratory animals
	Plant proteins	Flour
	Metals	Nickel
Hypersensitivity pneumonitis	Biologic dusts	Thermophilic actinomycetes
Pneumoconiosis	Mineral dust	Asbestos, silica, coal
Lung cancer	Mineral dust	Asbestos
	Metal dust	Arsenic
	Radiation	Radon

Many cases of OELD involve litigation, and a formal report containing the clinician's opinions is needed for dispute resolution (see Chapter 83). The clinician may be asked to rate the pulmonary disability using systems such as the American Medical Association Guides to the Evaluation of Permanent Impairment or the Black Lung Benefits Act. It is important to become familiar with the relevant rating systems and to use appropriate terms when describing disability caused by OELD. Reports that are imprecise or do not contain the appropriate language cannot be used to provide benefits for the patient.

The issues of occupational exposure and subsequent disease in a particular patient may provide the basis for interventions or screening programs to prevent or identify

Table 78.2. General approach to the patient suspected of having occupational-environmental lung disease

Medical and respiratory history
–Symptoms (e.g., dyspnea, cough, sputum, wheezing)
–Smoking
–Past medical history (e.g., asthma, atopy, cardiorespiratory diseases)

Detailed occupational history (see Table 78.3)

Physical examination
–Respiratory (e.g., wheezing, rales, rhonchi)
–Cardiac (e.g., coronary artery disease, congestive heart failure)
–Other (e.g., obesity, neuromusculoskeletal conditions, clubbing)

Laboratory data
–Chest radiographs (e.g., pneumoconiosis)
–Pulmonary function tests
–Special studies (e.g., serology, skin tests)

Industrial hygiene data
–Material Safety Data Sheets
–Air sampling data
–Site visit

Research—literature review
Report preparation—disability evaluation
Prevention

Table 78.3. Essential features of an occupational-environmental history

Chronologic list of all jobs, beginning with the first
Job activities and materials used for each position
Duration and intensity of exposure in each position
Protective equipment (e.g., respirators, gloves, aprons)
Adequacy of ventilation in workplace
Activities and materials used by coworkers
Health effects in coworkers
Parttime jobs
Domestic exposures (e.g., pets, hobbies)
Chronology of disease in relationship to work or environmental exposures

OELD in others. Recognition of a specific risk factor for OELD has often begun with an unusual case report. If involved with patients with OELD, consider whether hazardous exposures or working conditions could be altered and make recommendations when appropriate.

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79. SILICOSIS

Richard D. Drucker

Silicosis is a fibrotic disease of the lungs caused by inhalation of crystalline silicon dioxide. Silicon dioxide is a ubiquitous material that is a major component of the earth's crust. Three major crystalline forms of silicon dioxide are associated with lung injury: quartz, cristobalite, and tridymite. These forms are termed *free silica*, in contrast to silicates, which are crystals of silicon dioxide complexed with inorganic cations such as calcium, iron, magnesium, or aluminum. Silicates are also capable of inducing lung injury. Inhaled free silica particles greater than 10 μ in diameter are trapped in the upper respiratory tract, whereas particles 0.5 to 5.0 μ in diameter deposit in the alveoli and are pathogenic.

The classic occupations at risk for silicosis are mining (quarrying, tunneling), manufacturing (glass, pottery, porcelain, abrasives), and sandblasting. The development of disease appears to be related to the duration, concentration, and structure of the free silica dust in the environment as well as to the incompletely characterized individual susceptibility to silica inhalation. With improved dust control, the prevalence of the disease appears to be decreasing but sporadic cases still appear because of noncompliance with industrial hygiene standards, ignorance of the toxicity of silica dust, or unexpected exposures such as inhalation of scouring powder. Fortunately, only a few workers at risk actually develops silicosis.

The exact pathogenesis of silicosis remains unclear. Abundant evidence indicates that the pulmonary alveolar macrophage plays an important role in mediating lung damage. Silica particles are inhaled and ingested by the macrophage within the alveolus or within the interstitium. In vitro studies suggest that silica particles are isolated within intracellular phagosomes of the macrophage, which then acquire lytic enzymes from intracellular lysosomes. Within hours of particle ingestion, this phagolysosome ruptures and releases cytotoxic enzymes within the macrophage, thereby causing autodigestion of the macrophage, cell lysis, and release of the previously ingested silica particle. This cycle can then be repeated. More recent observations employing bronchoalveolar lavage fluid of silica-exposed animals and human workers have shown, however, that alveolar macrophages that contain silica appear structurally and functionally normal but demonstrate silica-induced release of inflammation mediators. It is hypothesized that silica stimulates the alveolar macrophage to release inflammation mediators that affect lymphocytes, polymorphonuclear leukocytes, fibroblasts, and other macrophages. Plasma cells are seen at the periphery of the early lesions of silicosis and are presumed to secrete immunoglobulins that moderate the cellular interactions. The interplay of these mechanisms is presumed to promote fibrogenesis with collagen deposition and eventual hyalinization. The properties of the silica particle that might catalyze these later events, such as the surface properties of the silica crystal and the formation of oxygen free radicals, are still under investigation.

The classic pathologic lesion of silicosis is the hyaline nodule, consisting of concentric whorls of connective tissue and an acellular central zone containing free silica. The middle zone has fibroblasts and collagen, and the active peripheral zone contains macrophages, fibroblasts, and free silica. The nodules are rounded and scattered throughout the lungs with predominance in the upper lobes. Simple nodules rarely compress airways or blood vessels, but large coalescent masses in the advanced stage

of silicosis can involve these structures. Regional lymphadenopathy and pleural adhesions are common, particularly in more severe cases of silicosis.

Three major clinical presentations of silicosis are described: chronic silicosis, accelerated silicosis, and acute silicosis. *Chronic silicosis* becomes clinically apparent 20 or more years after exposure to free silica. *Accelerated silicosis* becomes clinically apparent 5 to 15 years after exposure to heavier concentrations of silica. The presentations of chronic and accelerated silicosis are similar. Roentgenographic abnormalities usually antedate the development of symptoms such as cough, sputum production, and dyspnea on exertion. The third clinical presentation, *acute silicosis*, develops within 6 months to 2 years of massive exposure to free silica. It tends to have a fulminant course with cough, weight loss, rapidly progressive dyspnea, and early death. The disease was initially described as an interstitial fibrosis with minimal nodularity. Histologically, the alveoli are filled with a periodic acid-Schiff–positive acellular material that is similar to that seen in pulmonary alveolar proteinosis (silicoproteinosis). Extrapulmonary involvement (kidney and liver) has been described in acute silicosis.

Patients with silicosis have an increased incidence of mycobacterial infections. In one series of silicotic sandblasters, 25% had mycobacterial disease, one half of which were caused by nontuberculous mycobacteria. The incidence of such disease is greater in patients with acute or accelerated silicosis. It is important to keep a high index of suspicion for possible tuberculosis in patients with silicosis. In addition, a notable incidence is seen of nocardiosis, cryptococcosis, and sporotrichosis.

Compared with the general population, patients with silicosis have an increased incidence (10%) of collagen vascular diseases. Particularly prevalent are progressive systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. Clinically, the course of the collagen vascular disease is similar whether or not silicosis is present; however, the clinical course of silicosis is less favorable in those patients who also have a connective tissue disease. In silicosis, also is found an increased incidence of hypergammaglobulinemia, antinuclear antibodies, rheumatoid factor, and circulating immune complexes. No correlation, however, has been demonstrated between these serologic abnormalities and the clinical, roentgenographic, or physiologic presentation of the patient with silicosis. Angiotensin-converting enzyme levels are elevated in one third of patients with silicosis.

An unresolved issue is whether inhaled silica is carcinogenic. Multiple studies suggest that men with silicosis have a substantial risk of dying from lung cancer. All but one of these studies was confounded by significant epidemiologic variables and no definitive conclusion has been reached in this area.

Three main patterns of radiographic abnormalities are seen in silicosis. In *simple silicosis*, reticular and nodular patterns are frequent. The nodules range from 1 mm to less than 10 mm in diameter, predominate in the upper lobes, and usually have sharp margins. Hilar adenopathy is common. Of hilar nodes, 5% have the characteristic appearance *eggshell calcification*, which, although once considered to be pathognomonic of silicosis, has been reported in sarcoidosis and tuberculosis as well. *Progressive massive fibrosis* (also termed conglomerate or complicated silicosis) is characterized by densities that are 10 mm or larger in diameter that often seem to coalesce into larger masses. In *chronic silicosis*, the involvement is primarily in the upper lobes, in contrast with the lower and middle lobe predominance in the accelerated variant. Atelectasis is common in the involved lobes, with compensatory overexpansion of the remaining lobes. Although high resolution computed tomography can more clearly delineate the extent of parenchymal disease, it is not more sensitive than plain chest radiographs. Superimposed mycobacterial disease should be suspected in the presence of cavitation, pleural thickening, or rapid increase in nodule size. In silicoproteinosis, the chest roentgenogram has either a diffuse alveolar-filling pattern similar to pulmonary alveolar proteinosis or, less commonly, a reticulonodular pattern.

Pulmonary function abnormalities in silicosis are variable. Patients with simple silicosis who are asymptomatic usually demonstrate no abnormalities. Patients with progressive massive fibrosis show a restrictive, obstructive, or mixed pattern. Reductions in diffusing capacity, pulmonary compliance, and arterial oxygenation with exercise have been shown in patients with advanced stages of silicosis.

The diagnosis of silicosis is based on a history of exposure to free silica and a characteristic chest roentgenogram. Biopsy is indicated only in patients with atypical

roentgenograms or in a medicolegal dilemma (e.g., a compensation case involving multiple dust exposures). Open lung biopsy is preferred to percutaneous or bronchoscopic approaches. Hyaline nodules in various stages of development are characteristic. Doubly refractile particles can be seen with polarizing light microscopy, but these particles are not diagnostic of silicosis. In certain cases, x-ray energy spectrometry or scanning electron microscopy is needed for diagnosis.

No effective treatment of silicosis exists. Current efforts are aimed at disease prevention by limiting free silica exposure and by removing patients with silicosis from further exposure. The efficacy of corticosteroids is unproved, although an uncontrolled clinical trial has shown short-term improvement in chronic silicosis and a case report has shown improvement in acute silicosis. Whole lung lavage in silicosis has been used successfully to remove dust, but the clinical utility is not yet proved. Lung transplantation has been performed for patients with acute and accelerated silicosis.

In the preantibiotic era, most deaths from silicosis resulted from mycobacterial infections. Most current deaths from silicosis are attributed to progressive respiratory insufficiency. Patients with a significantly reactive tuberculin skin test should receive isoniazid chemoprophylaxis. Patients with concomitant connective tissue disease may require corticosteroids, whereas those with obstructive lung disease may require appropriate therapy for that disorder.

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80. COAL WORKERS' PNEUMOCONIOSIS

William G. Hughson

Coal workers' pneumoconiosis (CWP), formerly called *anthracosis* or *anthracosilicosis*, exists in two forms: simple and complicated. Simple CWP is diagnosed by a history of exposure to coal dust and chest radiographs showing an increased profusion of small, round parenchymal densities (categories 0, 1, 2, and 3 as rated by the International Labor Office system for grading radiographs for pneumoconiosis). Complicated CWP is known as progressive massive fibrosis (PMF). The diagnosis of PMF requires densities larger than 1 cm in diameter; some authorities require lesions larger than 2 cm.

The basic pathologic lesion in simple CWP is the coal macule. This is a collection of coal dust-laden macrophages, reticulin, and collagen located within the walls of respiratory bronchioles and adjacent alveoli. Macules range in size from 1 to 5 mm in diameter and are located predominantly in the upper lobes. As the number of macrophages grows, fibrosis increases, creating micronodules (<7 mm) and macronodules (7–20 mm). A zone of focal emphysema is usually seen around macules and nodules, possibly caused by mechanical traction on adjacent parenchyma or digestion of alveolar walls by proteolytic enzymes released from macrophages. A tendency is seen for nodules to cluster and eventually to coalesce to produce PMF lesions.

The pathogenesis of CWP is unclear. Silica in coal dust was thought to be the cause; it is now recognized that CWP is a pathologic entity distinct from silicosis, although the two conditions can coexist in the same individual. Coal is composed predominantly of elemental carbon and varying amounts of minerals, metals, and organic compounds. Electrically charged surface radicals on coal dust damage biologic membranes. Regional differences in the frequency and severity of CWP may be caused by the content of Fe^{2+} and buffering capacity of the dust. Higher rank (hardness) coals are associated with increased risk of simple CWP and PMF. Anthracite is the highest rank, followed by bituminous and lignite. Experimentally, high-rank coals are cleared more slowly from the lungs and are more cytotoxic. The attack rate for PMF rises with increasing total lung dust; PMF usually occurs in the setting of advanced simple CWP (categories 2 and 3). Increased silica content of inhaled dust also increases the incidence of PMF. Historically, tuberculosis has been considered as a risk factor for PMF; its role has diminished in recent decades, although this organism should always be sought in a patient with expanding upper lobe lesions. Cavitation of PMF lesions usually results from tissue necrosis, not tuberculosis. Coal miners do not have a greater incidence of tuberculosis compared with the general population.

The pulmonary macrophage plays a central role in the pathogenesis of CWP by releasing inflammatory factors, recruiting polymorphonuclear leukocytes into the lung, and stimulating fibroblast production of collagen. A number of immunologic abnormalities have been found in miners with CWP. Their causative role, if any, is unknown and their prevalence has varied in different studies. Miners with CWP have elevated serum levels of IgA, IgG, C3, antinuclear antibodies, rheumatoid factor, and α_1-proteinase inhibitor; similar findings are seen in other forms of pneumoconiosis. No clear correlation is found between these serologic factors and the risk or severity of CWP except for rheumatoid pneumoconiosis (Caplan's syndrome), which describes coal miners with rheumatoid arthritis. The characteristic radiographic features of rheumatoid pneumoconiosis are rapidly enlarging, evenly distributed nodules ranging in size from 0.3 to 5.0 cm in diameter, occurring in lungs that otherwise show little evidence of pneumoconiosis. Microscopically, the active lesions are similar to subcutaneous rheumatoid nodules; vasculitis is a common feature. Coal mining does not predispose to rheumatoid arthritis.

The risk of development and progression of CWP increases with cumulative dust exposure. Most affected miners worked before 1969, when the Federal Coal Mine Health and Safety Act (known as the Coal Act) was passed. It required that a coal worker's exposure to respirable dust be maintained at or below 2 mg/m^3. The Federal Mine Safety and Health Act of 1977 (known as the Mine Act) consolidated all federal health and safety regulations of the mining industry under a single statutory scheme, and created the Mine Safety and Health Administration for enforcement. Annual deaths from CWP have declined from nearly 3000 in 1972 to 1766 in 1992. However, new cases of CWP are still occurring, raising the issue of whether the current exposure limit is too high, or if enforcement is inadequate.

The issue of impairment and disability caused by CWP is controversial. Most authorities agree that clinically significant pulmonary impairment does not occur in nonsmoking patients with simple CWP, although small reductions in spirometric values are common. Conversely, PMF is associated with significant morbidity and premature death. Cough and sputum production, often described as industrial bronchitis, usually have little effect on lung function in the absence of smoking. Cigarette smoking, although responsible for most pulmonary impairment among coal miners, does not increase the incidence of simple CWP or the risk of progression to PMF. The Mine Act and Black Lung Benefits Program established guidelines for rating disability based on reduction of the forced expiratory volume in 1 second (FEV_1) and maximal voluntary ventilation. Decrements in spirometric values are based on a miner's height, but not age, and do not consider the effects of smoking. Should a miner have either a normal ventilatory capacity or a slight decrement, that person can still qualify for benefits if the Pa_{O_2} is reduced below a certain level with an alveolar-arterial oxygen gradient greater than 45 mm Hg breathing room air at rest. Exercise testing is not included in the rating system.

Today, the life expectancy of a coal worker approximates that of the general population. Excess deaths are seen for nonmalignant respiratory disease, accidents, and

possibly stomach cancer. Approximately 4% of coal worker deaths are directly attributable to pneumoconiosis, usually PMF; most studies have not shown an excess mortality for simple CWP. These excess deaths are counterbalanced by decreased mortality from lung cancer and ischemic heart disease. Employed populations typically have morbidity and mortality rates 10% to 20% lower than the general population, which contains individuals disabled by chronic diseases. This deficit of disease is referred to as the *healthy worker effect*. Cor pulmonale and right ventricular hypertrophy do not occur in the absence of cigarette smoking or PMF. No specific treatment exists for CWP except limiting dust exposure.

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81. ASBESTOS-RELATED DISEASE

Carolyn S. Ray

The term *asbestos* refers to a group of six naturally occurring, fibrous hydrated silicates that share a common property of resistance to heat and fire. Chrysotile, or white asbestos, which is characterized by serpentine fibrils, constitutes 90% of the asbestos used in North America. Amosite, crocidolite, anthophyllite, tremolite, and actinolite are used less often. These fibers have both carcinogenic and fibrogenic effects.

Exposure to asbestos poses a formidable challenge to public health officials. Between 1940 and 1979, an estimated 27,500,000 individuals were exposed occupationally in the United States alone. Recorded mortality from asbestosis has increased markedly from 1970 to 1990. This pattern of exposure and potential disease will continue as the asbestos already in place deteriorates and requires repair or removal. Exposure occurred most commonly in the occupations of asbestos mining and manufacturing; shipbuilding, repair, and refitting; general construction trades; automobile maintenance; and railroad engine repair. Other trades with significant occupational exposure include sheetmetal workers, foundry workers, electricians, carpenters, and cement workers. In addition, an increased incidence of asbestos-related disease is found among family members of asbestos workers and among workers employed in the vicinity of asbestos workers (*bystander exposure*). A significant risk for disease has not been reported among populations with only environmental or background exposure to asbestos. It is unclear whether a safe level (i.e., a threshold) for asbestos exposure exists below which no increased risk for cancer is seen. Extrapolation data suggest no minimal level; however, clinical studies indicate a relatively safe level may exist. Low-dose, long-term exposures are showing an increased incidence in asbestos-induced lung disease.

Asbestosis refers to parenchymal fibrosis; it occurs in up to 78% of heavily exposed insulation workers and up to 30% of those moderately exposed. Pathologically, asbestosis is characterized by the presence of interstitial fibrosis and an increased number of asbestos ferruginous *bodies* and uncoated asbestos fibers. The ferruginous body is an asbestos fiber coated with proteinaceous iron-staining material; it is visible on light microscopy. Using lung digestion techniques, uncoated fibers can be identified and counted; levels should be compared with those found in lungs of unexposed individuals to assess the significance of possible exposure in an individual. The range is wide and does not appear to correlate well with the type or degree of disease. The difference between environmental and occupational exposures, however, is clear.

Asbestosis usually begins subpleurally in the lung bases. As the disease progresses, it can involve both lungs diffusely as a fine fibrosis. In the final stages, the lungs can acquire a cystic honeycomb appearance (i.e., *honeycomb lung*) and can be indistinguishable radiographically from other forms of severe interstitial fibrosis. Recent experimental data suggest the fibrogenic response to inhaled asbestos fibers begins within hours of exposure. It is followed by macrophage-mediated immunologic, inflammatory, mechanical, and chemical injury at the alveolar level. A mild neutrophilic alveolitis ensues and interleukin-8 increases. This inflammatory mediator cascade can result in permanent fibrosis.

The clinical presentation of asbestosis is usually heralded by dyspnea. End-inspiratory rales and clubbing may be present with advanced disease. A clinical diagnosis of asbestosis requires an appropriate exposure history and a consistent latency period (i.e., the number of years from the initial exposure). The average minimal latency period for all forms of asbestos disease is approximately 20 years, but it can be as low as 10 to 15 years with no upper limit. Chest radiograph analysis using the International Labor Office system is useful to support a diagnosis; however, the lack of distinct findings does not exclude a diagnosis. Several clinicopathologic studies have demonstrated significant asbestosis on lung biopsy in 10% to 20% of patients with normal chest x-ray films. High-resolution, thin-section computed tomography scans (HRCT) are valuable in providing objective evidence of interstitial disease in the presence of normal, equivocal, or mild parenchymal abnormalities on chest radiographs. Studies have clearly demonstrated a relationship between disease on HRCT and lung tissue pathology.

Laboratory study is often helpful, although it occasionally demonstrates enigmatic findings. Pulmonary function tests may disclose diminished lung volumes (i.e., vital capacity and total lung capacity) and a decrease in single-breath diffusing capacity. Such abnormalities can be confounded by the countervailing effect of severe airways disease, a condition that tends to raise total lung capacity and which is found among a high percentage of asbestos workers because of their heavy tobacco smoking. Several large series have documented the effects of asbestos exposure alone on pulmonary function. In the absence of cigarette smoking, changes occur characteristic of both small airways dysfunction (obstruction) and restriction. The earliest pulmonary function test (PFT) abnormality is a decline in compliance (i.e., increased stiffness). Exercise testing is useful in

identifying clinically significant pulmonary disease among dyspneic individuals with relatively normal pulmonary function. The level of dyspnea often does not correlate with a single PFT value nor with a specific radiographic profusion score. The degree of impairment and disability should be noted according to subjective and objective criteria established by the American Thoracic Society and the American Medical Association.

Pleural disease or *pleural fibrosis* is the most common form of asbestos-related pulmonary injury. The incidence correlates primarily with disease latency. Pathologically, localized areas of pleural scarring (the pleural plaque) are seen. Calcification can occur and appears to be primarily related to the latency period. Calcification of diaphragmatic pleural plaques is a *sine qua non* of asbestos-related pleural disease. Pleural plaques viewed on a plain chest radiograph are usually bilateral and involve the middle and lower thirds of the thoracic cage. Chest CT scans demonstrate that up to one third of patients with asbestos pleural disease have unilateral abnormalities. Pleural plaques are generally found on the parietal pleural surface. Recent data from CT studies indicate that visceral plaques can also be present in fissures and the mediastinum. The usual pleural plaque does not lead to abnormal lung function; however, studies of groups of workers exposed to asbestos have shown a mild but significant decrement in vital capacity and FEV_1 with asbestos exposure, and asbestos pleural plaques alone. Extensive pleural plaques can lead to restrictive lung disease, particularly in cases of underlying parenchymal disease. Diffuse pleural thickening is a distinct process that leads to thickening or fibrosis of the visceral and parietal pleura. If extensive and severe enough, it results in lung entrapment and can lead to severe impairment and ventilatory failure. The most likely cause of *benign* diffuse pleural thickening is an initial asbestos-related pleural effusion. Subpleural fibrosis may also be present.

Rounded atelectasis is characterized by localized pleural thickening and lung entrapment. Before advances in CT scanning, pleural biopsy was necessary to distinguish this process from mesothelioma.

A variety of cancers are related to asbestos exposure. Lung cancer and mesothelioma are discussed in other chapters. In addition, an increased incidence of gastrointestinal cancers is seen, particularly gastric and colon, as well as pharyngeal, renal, and lymphomas. A a dramatic synergistic relationship exists between asbestos and cigarette smoking and the risk of lung cancers, excluding mesothelioma. Radiologic fibrosis or asbestosis is not a requirement for attributing lung cancer to asbestos exposure. Asbestosis is only one of several factors to consider in determining disease causation. The presence of benign asbestos pleural disease, increased levels of asbestos bodies in the lungs, or both may indicate an increased risk for the development of lung cancer. Lung cancers can occur as a result of asbestos exposure in the absence of clinical or histologic asbestosis. Mesothelioma is reported with even minimal asbestos exposure. No specific therapy exists for asbestos-related pleural or pulmonary disease. Common sense dictates the avoidance of any further exposure once injury is recognized. Every effort should be made to eliminate smoking. Other measures include early treatment of lung infections, influenza and pneumonia vaccinations, careful surveillance, and treatment of complications of respiratory failure.

Annual screening evaluations that include chest radiographs and PFT, and recent CT scans are important for selected patients. In view of the marked increased risk of cancer, each patient should be evaluated fully for any change in cough pattern, hemoptysis, or suggestive radiographic changes.

General Considerations

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82. OCCUPATIONAL ASTHMA

William G. Hughson

Asthma is a disorder of lung function characterized by widespread obstruction of the airways that (1) varies in severity; (2) is reversible, either spontaneously or as a result of treatment; and (3) is not caused by cardiovascular disease. Occupational asthma (OA) is causally related to exposure in the working environment to airborne dusts, gases, vapors, or fumes. Some definitions of OA require an immune-mediated sensitivity to a specific agent; however, also consider nonspecific irritants, because aggravation of pre-existing non-OA is usually compensable under workers' compensation. Asthma is a common disease. Approximately 10% of people will be diagnosed with asthma during their lifetime (i.e., the incidence of asthma). Some cases resolve, but approximately 5% of the population have active asthma (i.e., the prevalence of asthma). OA is responsible for 2% to 15% of asthma prevalence; the actual frequency varies widely between occupations and within industries at different levels of exposure. The true occurrence of OA is probably greater than reported because affected workers often terminate their employment, leaving unaffected survivors. This type of self-selection is common in studies of working individuals that compare morbidity and mortality rates with those of the general population. Employed populations typically have morbidity and mortality rates 10% to 20% lower than the general population, which contains individuals disabled by chronic diseases. This deficit of disease is referred to as the *healthy worker effect*. Because asthma is common in the general population and the clinical findings in OA are identical to those of non-OA, the challenge is to understand the nature and degree of workplace exposures and to make a temporal association between the asthma and occupation. Diagnosis can be difficult, given the inherent variability of asthma and the fact the patient can have early, late, dual, or recurrent late onset of symptoms.

The pathogenetic mechanisms of OA can be classified as reflex, inflammatory, pharmacologic, and allergic. *Reflex bronchoconstriction* involves irritant receptors in the airway that are stimulated by agents such as cold air, inert dust particles, gases, and fumes. The reaction does not involve immune mechanisms and is nonspecific. Many patients have a history of asthma. *Inflammatory bronchoconstriction* begins as a nonspecific reaction following inhalation of high concentrations of nonspecific irritants. Most individuals recover, but a few develop chronic asthma. This condition is often referred to as *reactive airways dysfunction syndrome*. Vocal cord dysfunction characterized by hoarseness, cough, and dyspnea is also caused by irritant exposures, and can be mistaken for asthma. *Pharmacologic bronchoconstriction* occurs when agents in the work environment exert a specific pharmacologic effect on the lung. An example is cholinesterase inhibition by organophosphate pesticides causing bronchoconstriction because of excessive parasympathetic stimulation. *Allergic bronchoconstriction* is the most common cause of OA. Susceptible workers develop IgE or IgG antibodies following exposure to workplace antigens such as animal or plant proteins. If high molecular weight compounds are responsible (e.g., baker's asthma), individuals who are atopic become sensitized more readily than workers who are nonatopic. However, atopy is not a predisposing factor when low molecular weight compounds are involved (e.g., isocyanate manufacturing). Sensitization takes time, and the latency period between exposure and the onset of symptoms can be weeks to years. Several hundred workplace agents have been shown to cause OA, and the list grows every year. Cigarette smoking doubles the risk of OA, possibly by recruiting inflammatory cells into the lung where they are available to react with irritants and sensitizers.

When considering OA as a diagnosis, two questions must be answered: First, does my patient actually have asthma? Second, is the asthma related to work? The general approach to diagnosing asthma is discussed elsewhere in this manual (see Chapter 46). Methods for answering the second question include a detailed clinical and occupational history, physical examination, chest radiographs, pulmonary function tests, inhalation challenge tests, and immunologic tests.

The *clinical history* of the patient with OA typically reveals shortness of breath, chest tightness, cough, and wheezing at work or within several hours after leaving work. Respiratory symptoms are often accompanied by rhinitis or conjunctivitis. Recurrent attacks of *bronchitis* are often reported. Improvement on weekends, vacations, or when away from work is an important clue. Patients, who develop symptoms immediately after exposure or whenever they work with the same material, usually recognize a causal relationship. However, a large number of substances, particularly low molecular weight organic and inorganic compounds, may give rise to late asthmatic reactions. Nocturnal attacks of dyspnea and cough may be the only manifestation of OA, thus, be aware that the onset of symptoms may not be simultaneous with workplace exposure. Key elements influencing the pattern of symptoms and airflow obstruction seen in workers with OA are the recovery time and the effects of cumulative exposures. Some individuals improve rapidly after leaving work, and recovery is virtually complete before the next workday. Such workers show a similar deterioration during each shift. At the other extreme are those who need more than 2 days to recovery. Repeated exposures over several weeks, even with weekends off, result in a steady deterioration of pulmonary function. Clinical features can be indistinguishable from chronic obstructive lung disease because of nonoccupational causes. The reactive nature of the disease can be masked by a fixed reduction in expiratory flow rates seemingly unrelated to work activities. In such cases, the true relationship between the patient's occupation and asthma becomes apparent only after prolonged cessation of exposure allows sufficient time for recovery of normal pulmonary function. When the patient finally returns to work, the simultaneous reappearance of symptoms and airflow obstruction makes the link obvious.

The *occupational history* is crucial for the diagnosis of OA. Obtain a detailed description of the patient's work practices, including the agents used, protective equipment such as respirators and gloves, and the adequacy of ventilation. In addition to the patient's own work, information concerning other processes and chemicals used by coworkers should be obtained; bystander exposures can cause reactions in sensitized individuals. It is often helpful to ask whether coworkers have similar problems. Patients usually have only limited knowledge of the agents they use. Material Safety Data Sheets should be obtained from the employer, who is legally required to provide them to the worker. If the clinician is careful to avoid a confrontational situation, the employer or the workers' compensation insurance company may provide industrial hygiene data concerning the nature and degree of exposures. Site visits are often helpful, and the clinician must be prepared to search the medical literature to complete the assessment.

The *physical examination* may reveal conjunctivitis, rhinitis, and wheezing; however, these signs are often absent, particularly when the patient has been away from work for some time. The chest radiographs are usually normal in patients with OA, although parenchymal infiltrates and hyperinflation may be seen.

Pulmonary function tests (PFT) should demonstrate expiratory obstruction and hyperinflation, with improvement following inhalation of bronchodilator medication. However, variability of airway obstruction is a key feature of asthma, and the PFT may be normal. In this situation, the demonstration of bronchial hyperreactivity (BHR) depends on provocation tests using methacoline, histamine, cold air, or exercise as a stimulus. These nonspecific promoters of BHR cannot identify a workplace cause. The *gold standard* for diagnosing OA in the pulmonary laboratory is a specific inhalation challenge using the suspected agent. However, it is often difficult to select the correct chemical from among many used in the typical, complicated workplace environment. In addition, practical difficulties exist to administering the correct concentration of the agent and few facilities have sophisticated environmental chambers. Pre- and postshift PFT measurements may demonstrate expiratory obstruction after workplace exposures. Another approach is

patient is provided with an inexpensive flow meter and maintains a diary during the workweek, evenings, and weekends. At least 2 weeks of observation are needed. This requires considerable patient cooperation, and the results of self-administered tests are often suspect in the setting of potential litigation and secondary gain. Some authors have recommended serial measurements of BHR using methacholine before and after work shifts; decreased provocative dose following exposure is supportive of OA.

Skin tests and serology may be useful in identifying specific sensitization. However, selection and preparation of agents for skin testing is difficult, and nonspecific irritation can lead to false-positive findings. Antibody assays are available for only a limited number of workplace chemicals; positive serology indicates previous exposure, but is not diagnostic of asthma caused by that agent. Skin tests and serology may suggest the cause of OA but are not definitive.

The *treatment* of OA is identical to that for non-OA. Emphasis should be placed on avoidance of the agent responsible in sensitized individuals and reduction in exposure to nonspecific irritants. The *prognosis* of patients with OA is guarded. More than 50% will remain symptomatic a year after removal from exposure. The clinician will often be asked to define disability caused by OA. This requires a careful assessment of the degree of airflow obstruction and BHR and whether the patient could return to work with certain restrictions or job modifications. If return to work is not feasible, vocational rehabilitation is required. These decisions require input from the clinician, patient, employer, and the agency responsible for administering workers' compensation claims.

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83. DISABILITY AND MEDICOLEGAL EVALUATION

William G. Hughson

Many physicians dislike medicolegal report writing. They are more comfortable with their traditional role of diagnosing and treating disease. However, providing clearly written reports is essential in helping patients obtain appropriate workers' compensation and other benefits. These reports are used by nonmedical personnel such as disability raters, insurance claims adjusters, and workers' compensation judges; consequently, these reports often require the use of special forms and obscure terms to achieve specific legal and administrative goals. A properly written report can facilitate clear communication between the physician and these nonmedical professionals.

It is important to distinguish between impairment and disability. *Impairment* describes an anatomic or functional loss caused by a disease process. *Disability* describes the effects of the impairment on the patient's life, including the ability to work. It can be defined as the inability to perform at a specified level of activity, or as undue distress during the performance of that task. The degree of disability is directly related to the physical requirements of the job. For example, a teacher with a forced expiratory volume in 1 second (FEV_1) of 1 L might have no disability, whereas a general laborer would need retraining for another job. Nonmedical people who rely on the physician's opinions make the final decision regarding disability.

A properly written medicolegal report should contain all of the sections found in a typical medical consultation plus a detailed occupational history. A patient-generated form that is completed before an examination may facilitate the latter. The assessment section of the report should contain answers to all of the questions listed in Table 83.1. We favor a *question-and-answer* format because it saves time and allows a clearer explanation of the issues and the physician's opinion. The key points that are discussed in each question apply to almost all reports.

What is the diagnosis? This is generally the easiest question to answer. Each lung condition should be listed along with the evidence supporting its diagnosis. For example, the diagnosis of asbestosis is based on a history of exposure, appropriate latency, the presence of interstitial markings on the chest radiograph, pulmonary function tests showing a restrictive pattern and reduction in the diffusing capacity, and crackles on

Table 83.1. Questions to be answered in a disability evaluation report

1. What is the diagnosis?
2. Is the diagnosis work-related by causation, aggravation or precipitation?
3. Is there evidence of impairment? If so, how severe is the impairment? What rating system is used, and how do the patient's findings correspond to this system?
4. Is temporary disability present? If so, is it partial or total? What is the anticipated time of recovery?
5. Can the patient return to his/her previous occupation? Could the patient return to the job if it were modified? Are there any work restrictions or preclusions?
6. Is permanent disability present? If so, is the patient stationary for rating purposes? When did the patient become permanent and stationary?
7. How severe is the disability? What rating system is used, and how do the patient's findings correspond to this system?
8. Are there permanent work restrictions? If so, what are they?
9. Is there any basis for apportionment of the permanent disability? If the work injury had not occurred, would a pre-exiting condition contribute to the disability?
10. Is vocational retraining indicated? If so, which types of jobs are appropriate?
11. Is further medical treatment needed? If so, what is the nature, frequency, and duration of the treatment?

physical examination. Nonpulmonary diagnoses should also be listed, particularly those affecting impairment or disability.

Is the diagnosis work-related? This requires a judgment that the disease was caused, aggravated, accelerated, or precipitated by a workplace exposure. *Causation* is defined as a new disease that has been caused by work (e.g., an insulator with asbestosis). *Aggravation* means a pre-existing condition that did not interfere with work or usual activities that is now worse because of employment (e.g., chronic obstructive pulmonary disease in a smoker exposed to industrial dusts). *Acceleration* means a pre-existing condition that would naturally worsen with time and that deteriorated more rapidly because of employment (e.g., airway obstruction in a patient with emphysema exposed to fumes). *Precipitation* means a pre-existing condition that became manifest for the first time because of employment (e.g., asthma in an atopic patient exposed to flour). The time sequence of the disease in relation to emplcyment is very important. For example, pneumoconiosis takes years to develop, and immune-mediated reactions require weeks to months before sensitization occurs. It is important to note whether symptoms are worse at work, and then improve on weekends or vacations. The presence of similar problems in coworkers is highly suggestive. The nature and severity of exposure should be determined by obtaining Material Safety Data Sheets and available industrial hygiene information. The use of protective devices (e.g., respirators) and adequacy of ventilation should be described.

Is there evidence of impairment? If so, how severe is the impairment? Subjective data (e.g., dyspnea, weakness, and pain) must be differentiated from objective data because symptoms are often unreliable measures of disease in the setting of litigation. The physical examination and chest radiographs provide diagnostic information, but are not useful in measuring function. Basic spirometry remains the cornerstone for assessing impairment. Other techniques (e.g., exercise testing) are added as necessary. It is important to know which rating system applies to the patient's case. The American Medical Association's (AMA) *Guides to the Evaluation of Permanent Impairment* is the one most commonly used. The referral source should give clear instructions and provide the rating system to the physician when necessary.

Is disability present? If so, is it partial or total, temporary or permanent? The key question: *Can the patient return to the usual and customary activities of employment*? This requires a clear understanding of the patient's work, including the physical effort needed and the potentially harmful exposures. The work history can be obtained from

the patient, supplemented with a written job description provided by the employer. Partial disability exists when the patient can perform some, but not all, of the usual job responsibilities. Useful questions include: *Could the patient return to the job if it were modified? Are there any work restrictions or preclusions?* In most states, the employer is required to make reasonable accommodations. However, job modification is often difficult, and the definition of *reasonable* can be contentious. Total disability exists if the patient is completely unable to perform the job, even with accommodation. If the disability is temporary (either partial or total), it is important to provide both the patient and the employer with an estimate of the time needed for recovery. This allows assignment of tasks to other workers. If permanent disability is likely, it is wise to advise both the employer and patient as soon as possible. This facilitates realistic planning for the patient's future.

If permanent disability is present, is the patient stationary for rating purposes? How severe is the disability? The patient is permanent and stationary for rating purposes after maximal medical improvement has been achieved and no prospect is seen for further recovery. The report should include a lucid description of the patient's impairment and its impact on work capacity. This includes any permanent restrictions and preclusions, but caution is warranted. Sweeping statements such as "No further exposure to dusts or fumes" may make the patient unemployable. Precision is needed, with a description of any specific precluded exposures (e.g., allergens or sensitizers) and consideration of dose (e.g., respirator use, ventilation requirements, Occupational Safety and Health Administration-permissible exposure limits). For example, an insulator with mild asbestosis might be able to continue working under current regulations, because permissible dust levels are now very low. The description of permanent disability must contain terminology appropriate for the rating system that applies. For example, in California words such as "minimal" or "moderate," "occasional" or "frequent" have specific meanings when used to describe dyspnea. The California Labor Code has categories such as *Disability precluding heavy work* and *Standard ratings* with percent disability caused by pulmonary disease. Copies of rating systems can be obtained from the referral source or from state and federal regulatory agencies.

Is there any basis for apportionment? Apportionment is only considered when permanent disability is present. It is used to describe the relative contribution of occupational and nonoccupational lung diseases to the total disability. However, the medical concept of apportionment differs from the legal principle, just as impairment differs from disability. For example, whereas most physicians would consider pre-existing asthma as a factor in a painter with pulmonary impairment, the legal concept of apportionment is concerned only with pre-existing disability. A useful question is: *If the work injury had not occurred, would the pre-existing condition contribute to disability?* In the case of the painter, if no evidence was found of disability before the injury at work (e.g., work restrictions, prior job loss due to the condition), no basis would be seen for apportionment, and the entire disability would be considered work-related. If a pre-existing condition causing disability is aggravated or accelerated by employment, the increment in disability is apportioned and is compensable. The best way to deal with apportionment is to dictate two paragraphs describing the permanent disability. The first describes existing disability factors (subjective and objective) and work restrictions. The second describes disability factors and work restrictions that would have existed without the occupational injury. The hearing officer then decides the extent of disability represented by each of the two paragraphs and, by subtraction, allocates the disability caused by employment.

Is vocational retraining appropriate? Patients with severe impairment may be totally disabled from any type of employment. Those with better function are suitable for retraining, which is a worker's compensation benefit. The physician should describe the types of jobs and work preclusions suitable for the patient. The physician may be asked to communicate with vocational rehabilitation counselors regarding the patient's condition.

Is further medical treatment needed? It is important to describe the nature, frequency, and anticipated duration of all treatment. In most instances, the cost of medical care is paid by workers' compensation if employment has contributed to disability, even when nonoccupational factors are present. Apportionment of medical costs is usually not allowed.

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84. PULMONARY COMPLICATIONS IN BURN PATIENTS

Deborah Ann Hoffman

Pulmonary complications account for most deaths in burn victims. Pneumonia, tracheobronchitis, inhalation injury, aspiration, and acute respiratory distress syndrome are the predominant pulmonary manifestations. Carbon monoxide and cyanide poisoning can further complicate the course of the burn patient, particularly in the setting of a closed space fire.

Pneumonia accounts for most deaths in fatally burned patients. When it occurs within the first week of hospitalization, aspiration or infection by community-acquired pathogens generally is responsible. In contrast, nosocomial pneumonia usually results from gram-negative bacilli, staphylococci, or fungi and may be acquired via hematogenous spread from infected wounds. Tracheobronchitis is diagnosed by the constellation of fever, purulent sputum, and microorganisms and neutrophils seen on Gram's stain, in the absence of pulmonary infiltrates. Tracheobronchitis often progresses to bronchopneumonia, especially in patients with inhalation injury.

The presence of inhalation injury has important implications for prognosis in the burn patient. In patients with similar external burns, inhalation injury increases mortality eight- to tenfold. Inhalation injury should be suspected when the patient sustains injury in a closed space, gives a history of inhaling smoke, has evidence of smoke particulate matter in the oropharynx, or has impaired consciousness. The extent of injury depends on the types of gases inhaled, size of particulate matter inhaled, and duration of exposure. Clinical signs of inhalation injury include wheezing, cough, hoarseness, dyspnea, bronchorrhea, stridor, and production of carbonaceous sputum.

Initial evaluation should include bronchoscopy to assess the degree of injury as well as to remove particulate matter. Inspect the mucosa for edema, erythema, sloughing, and carbonaceous debris. Patients with significant injury should be considered for elective intubation because airway edema and parenchymal damage with vascular permeability typically progress over 24 to 48 hours after exposure. In addition, massive amounts of fluids are typically administered in the first 24 hours to avoid burn shock, which may contribute to edema of the injured airway and jeopardize respiration. When burns involving the head and neck compromise the airway, intubation is performed to ensure adequate ventilation and oxygenation.

Inhalation injury results in both direct injury to the airways and lung parenchyma (local irritants) and to systemic injury secondary to anoxic effects of the products of combustion (systemic asphyxiants). Thermal insult to the airways does not cause subglottic injury. Rather, the inhalation of particulate matter with toxic products of combustion is responsible for mucosal irritation and injury. The caustic products of combustion that result in such injury include ammonia, hydrogen chloride, chlorine, nitrogen oxides, ozone, phosgene, sulfur dioxide, aldehydes, acrylonitriles, and anhydrides. Neutrophils are activated and produce a variety of cytokines, oxygen radicals, and proteolytic enzymes that act locally and systemically to produce tissue damage, increased capillary permeability, and subsequent noncardiogenic pulmonary edema or acute respiratory distress syndrome. Particulate matter, necrosis, and airway edema cause sloughing and formation of bronchial casts, which can lead to bronchospasm and airway obstruction. In addition, abnormal mucociliary clearance predisposes to atelectasis and pneumonia. Extensive chest wall burns can lead to restriction and reduce chest wall compliance, contributing to atelectasis and infection.

Therapy is supportive. β-agonists may be of benefit, but response is not uniform. Aminophylline, which is infrequently mentioned in the literature, can be used if bronchodilators are not effective. Steroids are not used in inhalation injury because they have been shown to increase the risk of mortality and infection. Chest wall escharotomies are performed to relieve restriction in patients with extensive chest wall burns. Usually, patients who recover after severe inhalation injury exhibit normal lung function, although long-term sequelae, including pulmonary fibrosis and bronchiectasis, may develop.

Asphyxiants are not directly toxic to the airway or lung parenchyma. Instead, these compounds exert their toxic effects by systemic distribution and interference with cellular respiration. Asphyxiants include carbon monoxide (CO), cyanide, methane, helium, and nitrogen. In closed-space fires, CO can quickly attain concentrations of 0.1%, associated with blood carboxyhemoglobin (COHb) levels of 50% to 60%. Carbon monoxide inhalation results in asphyxiation via displacement of oxygen from hemoglobin, left shift of the oxyhemoglobin dissociation curve, which results in impaired oxygen unloading in the tissues, and blockage of oxidative phosphorylation. In the initial evaluation of the burn patient with inhalation injury, the COHb level should be determined from an arterial blood sample to guide the need for a high concentration of inspired oxygen. It should be remembered that cutaneous oximeters do not measure COHb levels. The half-life of COHb with room air breathing is 3 to 4 hours. This is reduced to 30 to 40 minutes when 100% oxygen is administered, and 20 minutes with hyperbaric oxygen. Mild CO poisoning (5% to 30% COHb) manifests as psychomotor slowing, headache, nausea, and weakness. Concentrations of 30% to 40% COHb produce vomiting, syncope, and severe weakness. High levels (>50%) are associated with coma, seizures, dysrrhythmias, and death. Cherry red lips are a subtle but unreliable sign of CO poisoning. Benefit in outcome with hyperbaric therapy is controversial.

Cyanide poisoning occurs with combustion of nitrogen-containing (polyurethane) materials such as plastic and acrylic; typically, it occurs in association with CO poisoning. Cyanide disrupts cellular respiration and inhibits adenosine triphosphate generation. An elevated lactate level with severe metabolic acidosis has been shown to be a sensitive indicator of cyanide poisoning. Symptoms include headache, confusion, and lethargy reflecting anoxia. Cyanide is detoxified by the liver and requires sulfur as a substrate. Specific therapy for cyanide poisoning is controversial because of the difficulty in assessing clinically significant exposure and the fact that cyanide levels do not correlate with mortality. However, antidotes may be indicated in the setting of fires involving polyurethanes that produce large amounts of cyanide gas or in the burn

victim with severe, unexplained metabolic acidosis. Treatment options include chelators (cobalt edetate and hydroxocobalamin), sulfate to accelerate cyanide degeneration (sodium thiosulfate), and production of methemoglobin (from sodium and amyl nitratemoglobin), which combines with cyanide to form nontoxic cyanomethemoglobin.

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85. HYPERSENSITIVITY PNEUMONITIS

Dominic A. Munafo, Jr.

Hypersensitivity pneumonitis (HP), also known as *extrinsic allergic alveolitis*, results from the immunologic response to various inhaled biologic and chemical antigens. Ramazzini first described HP in 1713 as an acute respiratory syndrome seen in workers who handled improperly dried cereal grains. In 1932, Campbell published the classic description of farmer's lung, which results from the inhalation of spores of thermophilic actinomycetes, usually *Saccharopolyspora rectivirgula*. Additional antigens include fungi, various animal and insect proteins, and chemicals such as isocyanates

and anhydrides. Rarely, drugs such as amiodarone, gold, minocycline, methotrexate, and nitrofurantoin serve as haptens and become antigenic after combining with host proteins. Inhaled antigens are typically 1 to 5 μm in size; therefore, the site of lung injury is the distal airway and alveolus. An antigen's ability to trigger an immune response depends on its solubility, its resistance to digestion by macrophages, and its properties as an immunologic adjuvant. As many as 50% of heavily exposed individuals may develop antibodies to an inhaled antigen, but only a small percent will actually develop disease. Prevalence rates have been estimated at 5% to 15% in an exposed population and appear to depend on antigen type and host susceptibility.

Most cases occur through occupational, environmental, or avocational exposures. Historically, the various disease entities have been named for the circumstances in which the exposure occurs. Examples of HP include farmer's lung (thermophilic actinomycetes in moldy hay), pigeon-breeder's lung (serum proteins in pigeon droppings), bagassosis (bagasse in sugar cane), maple bark disease (fungi in moldy bark), and humidifier lung (amoebae in humidifier water).

Hypersensitivity pneumonitis can present in an acute, subacute, or chronic form. The *acute disease*, which is the most common form, occurs after an individual has had a previous sensitizing exposure to a particular antigen. Approximately 4 to 6 hours following re-exposure, the individual experiences the abrupt onset of a flulike syndrome. Symptoms include a nonproductive cough, fever, chills, dyspnea, myalgias, and malaise. The most prominent physical findings are tachypnea, tachycardia, and bibasilar inspiratory crackles. Wheezing is an uncommon finding. These signs and symptoms typically persist for 18 to 24 hours following exposure and then spontaneously remit. Symptoms will recur with each subsequent exposure; their severity will depend on the intensity and duration of exposure as well as the degree of a particular individual's sensitivity. The subacute and chronic forms of the disease result from chronic exposure to lower levels of antigen. Symptoms can be mild or absent and disease progression insidious. Continued exposure is associated with increasing dyspnea, cough, anorexia, and weight loss.

Laboratory findings are largely nonspecific. IgG serum precipitating antibodies to the offending antigen are present in most patients. IgA and IgM antibodies have also been described. Immunoglobulin levels are usually elevated in both serum and bronchoalveolar lavage (BAL) fluid; however, IgE levels remain normal. The presence of precipitating antibodies is not diagnostic of disease but only indicates previous significant exposure. Smokers have a lower incidence of antibody production. A leukocytosis with a left shift typically accompanies acute episodes. Eosinophilia is uncommon and should suggest the possibility of another diagnosis. Rheumatoid factor has been detected in more than 50% of patients experiencing repeated episodes. BAL shows a dramatic increase in the number of T lymphocytes recovered. Selective expansion of the $CD8^+$ subset occurs as does reversal of the $CD4^+$:$CD8^-$ ratio. This is in contrast with the findings in sarcoidosis in which the cells are predominantly $CD4^+$. Elevation of $CD8^+$ cells may be associated with less chance of progressive fibrosis. Although the percentage of alveolar macrophages recovered is markedly reduced, the absolute number of macrophages is near normal. BAL findings are not diagnostic of HP but rather serve to support the diagnosis and help to rule out other processes.

Histologically, a neutrophilic alveolitis in the first 24 hours gives way to an intense peribronchial inflammatory infiltrate of lymphocytes, plasma cells, macrophages, and giant cells. Noncaseating granulomas and refractile foreign bodies are often seen in the interstitium. In chronic disease, both granulomas and interstitial fibrosis are seen. Bronchiolitis obliterans is found frequently with or without organizing pneumonia. Vasculitis is not present.

The chest radiographic findings of HP are highly variable. Acutely, radiographs may be normal or show bilateral, ill-defined alveolar and interstitial nodular infiltrates. The distribution can be patchy or diffuse, with some predilection for the lower lobes. Hilar adenopathy and pleural effusions are rare. In *chronic disease*, the chest radiograph shows a reticulonodular pattern with interstitial fibrosis, honeycombing, and loss of lung volume. The fibrotic changes are often more prominent in the upper lobes and periphery of the lung. High-resolution computed tomography (HRCT) is more sensitive than chest radiography in demonstrating the characteristic centrilobular nodules and emphysematous changes; however, its sensitivity and specificity appear to vary, depending on disease severity and chronicity.

Pulmonary function tests during an acute episode usually show a restrictive defect. Mild to moderate hypoxemia, hypocapnia, and a decrease in the diffusing capacity of lung for carbon monoxide (DLCO) are often present. As many as 60% of patients will demonstrate airway hyperreactivity as detected by methacholine challenge. Patients who experience recurring attacks most commonly develop airway obstruction and a persistent decrement in DLCO. Progressive restriction secondary to interstitial fibrosis may also be seen. Cessation of exposure, early in the disease process, will lead to gradual resolution of the pulmonary function abnormalities over days to weeks. In *advanced disease*, progressive pulmonary insufficiency, chronic hypoxemia, and cor pulmonale may develop.

The diagnosis of HP is suggested by a history that relates symptoms to exposure, but may be particularly difficult in those patients with chronic low-level exposure. Most of the signs and symptoms of disease are nonspecific. The proposed six major diagnostic criteria include (1) compatible signs and symptoms; (2) appropriate exposure history; (3) consistent radiographic findings; (4) lymphocytosis in BAL; (5) appropriate histology on biopsy; and (6) positive inhalation challenge. The diagnosis is made when four of these criteria are met. Inhalation challenge, either in a laboratory setting or by returning the patient to the site of exposure, is the most specific diagnostic test. In the absence of an identifiable cause and in more chronic presentations, lung biopsy may be necessary to define the pathology and rule out other possibilities. Skin tests are not helpful. Differential diagnosis in the acute setting includes atypical and viral pneumonia, collagen vascular disease, organic dust toxic syndrome, and other acute inhalational injuries. In those patients who wheeze, consider occupational asthma, allergic bronchopulmonary aspergillosis, and byssinosis. Chronically, miliary tuberculosis, sarcoidosis, fungal infection, eosinophilic granuloma, and idiopathic pulmonary fibrosis can mimic HP. As many as 10% of referrals to some tertiary centers for idiopathic pulmonary fibrosis demonstrate pathology suggestive of HP. Therefore, a detailed exposure history in a patient with interstitial lung disease is essential.

The immunologic mechanisms responsible for HP have proved complex and are incompletely understood. Although both humoral and cellular immunity are involved, more recent investigations indicate that cell-mediated immunity is likely the more consequential. The acute alveolitis seen hours after antigen exposure is thought secondary to precipitation of immune complexes in the alveoli and interstitium. This type III immune response activates complement, resulting in an increase in vascular permeability and recruitment of additional inflammatory cells. Activated macrophages secrete a variety of proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1 (IL-1), and IL-12. Recent work in a murine model of HP has shown that interferon-γ (IFN-γ) is essential in the formation of granulomatous inflammation. Additionally, IL-10 appears to mitigate the inflammatory response to antigen and IL-12 appears to promote disease expression. Interestingly, IL-10 inhibits expression of IFN-γ and IL-12 enhances IFN-γ production. These data, coupled with studies showing adoptive transfer of HP using Th1-type cells, suggest that differences in regulation of this type IV immune response may help explain the varying clinical presentations of disease. Bronchus-associated lymphoid tissue can serve as a site of induction and amplification of the local immune response. Of note, common respiratory viruses have been found in the lower airways of patients with HP. In addition, studies in the murine model suggest that viral infection can augment the inflammatory response in HP. The significance of these findings remains to be seen.

The mainstay of therapy is avoiding exposure to the offending antigen. A less desirable alternative is the use of a mask or other filtration technique to substantially reduce or prevent exposure. The symptoms of subacute and chronic progressive disease can be indolent. Thus, if continued exposure is unavoidable, close follow-up with pulmonary function tests and radiographic studies is essential to assess disease activity. In some settings, patients may tolerate continued exposure without persistent symptoms or disease progression. On the other hand, some patients with pigeon-breeder's lung have developed progressive disease despite complete antigen avoidance. Currently, patients should be advised to avoid antigen exposure to the greatest extent possible. The use of corticosteroids in the acute setting often speeds recovery and decreases symptoms. In addition, some patients treated with corticosteroids develop

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86. NEAR-DROWNING AND DIVING ACCIDENTS

Tom S. Neuman

Accidental drowning occurs in all age groups, but is most common in children aged 1 to 4 years. Approximately 90,000 episodes of near drowning and 7000 to 9000 drowning-related deaths occur annually in the United States. A recent decline in the number of fatalities may reflect better prevention because of enhanced private pool safety.

Historically, the pathophysiology of near-drowning was thought to be an electrolyte disturbance induced by the aspiration of fluid. Current data suggest that hypoxemia is the major pathophysiologic abnormality and that electrolyte disturbances play a minor role, if any. In 10% to 15% of cases, hypoxemia appears to be secondary to simple asphyxia. In this group, little or no aspiration takes place. It has been hypothesized that reflex laryngospasm prevents aspiration; however, no experimental evidence supports this hypothesis. In this group, a relatively quick and uncomplicated recovery can generally be anticipated as ventilation is re-established unless protracted anoxia results in irreversible circulatory collapse or permanent neurologic damage. In the other 85% to 90% of cases, the hypoxemia is related to aspiration. The exact amount of fluid aspirated by victims remains unknown. In animal models that appear to duplicate the injury seen in human near-drowning victims, the amount of fluid instilled is generally 1 to 10 ml/kg. The mechanism of hypoxemia depends on the nature of the fluid aspirated. With seawater aspiration, osmotic and irritative effects from sand, diatoms, algae, and other particles provoke an exudative response. This exudate fills alveoli and results in ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch and hypoxemia. With fresh water aspiration, pulmonary surfactants are lost from the lung, leading to focal collapse, ($\dot{V}/\dot{Q}$) mismatch, and hypoxemia. When water is instilled into the trachea of experimental animals, pathologic studies reveal severe damage to alveolar and endothelial cells, as well as disruption of the capillary basement membrane.

The clinical manifestations of near-drowning vary with the degree of injury. A range of neurologic presentations can occur, reflecting variable degrees of cerebral anoxia. Pulmonary injury may be mild, manifesting as cough and mild shortness of breath, or it can be severe, resulting in fulminant pulmonary edema and acute respiratory distress syndrome.

Laboratory studies generally reveal hypoxemia and metabolic acidosis and perhaps a superimposed respiratory acidosis as well. Minor changes in electrolytes are seen frequently; however, clinically significant alterations in serum sodium or potassium are distinctly unusual in near drowning in either fresh or seawater. Chest x-ray studies may display a spectrum of abnormalities, ranging from patchy infiltrates to dense pulmonary edema. Occasionally, massive particulate aspiration can also occur. It has been hypothesized that the pulmonary edema occasionally seen in near-drowning victims is caused by negative pressure (attempting to breathe against a closed glottis) or to neurogenic factors.

The management of near-drowning patients is mainly supportive. Arterial blood gases should be monitored frequently and mechanical ventilatory support should be initiated if acute respiratory failure develops that is unresponsive to oxygen supplementation. Patients developing acute respiratory failure frequently require high ventilator pressures to provide adequate oxygenation and ventilation, reflecting a marked reduction of pulmonary compliance. The use of positive end-expiratory pressure during mechanical ventilation has proved beneficial in reducing both morbidity and mortality. Generally, ventilatory support is necessary for only a short time. Because mechanical ventilation is not benign, it is probably preferable to attempt other less invasive methods of ventilatory support (nasal continuous positive airway pressure or bilevel positive airway pressure, BIPAP) before intubation. The initial administration of hypertonic or hypotonic intravenous fluids is not warranted, because changes in electrolytes are usually minor. The use of antibiotics in the near-drowning victim who aspirates ocean or swimming pool water is usually restricted to those who develop fever, new pulmonary infiltrates, purulent secretions, or a combination thereof. Clinically, prophylactic antibiotics do not seem to improve mortality or decrease morbidity. Because most pulmonary infections in the near-drowning victim appear to be hospital-acquired, prophylactic antibiotics may only select for more resistant organisms. In addition to clinical experience, experimental evidence also indicates that prophylactic antibiotics are not indicated. In the unusual circumstance where the victim aspirates heavily contaminated water with a known organism, the use of prophylactic antibiotics may be appropriate.

Routine bronchoscopy to search for particulate matter causing airway obstruction is probably not necessary. Adrenocortical steroids used to treat the lung injury associated with near drowning are also probably unwarranted. Experimental evidence in this form of aspiration, as well as others, strongly suggests that steroids do not improve the

long-term outcome or short-term morbidity. One uncontrolled report (four cases), however, suggests high-dose steroids may be beneficial in near-drowning victims who present with pulmonary edema. The use of surfactants to treat near-drowning victims has been reported recently. It is unclear whether such therapy alters the outcome. In an experimental model, surfactant therapy did not offer any benefit over traditional ventilatory support.

Pneumothorax, lung abscess, and empyema often complicate the course in near-drowning patients with significant respiratory failure. Hypothermia at the time of the immersion incident can also complicate the picture. Although renal failure and disseminated intravascular coagulation have been reported, they are probably sequelae of prolonged acidosis, hypoxemia, and hypotension, rather than specific complications of near drowning.

The victim's prognosis depends primarily on the extent and duration of the hypoxemic episode. Age of the patient and prior illnesses can be modifying factors. Epidemiologic data do not support the hypothesis that cold water immersion improves the prognosis of the near-drowning victim. Rare, well-documented cases, however, report on near-drowning victims, who fully recover after prolonged submersion incidents in cold water. Many observational studies have been published attempting to better define prognostic factors for the near-drowning victim. Unfortunately, no factors seem to be completely reliable. In general, patients who present with a normal chest radiograph or normal mental status can be expected to survive without sequelae.

Most large studies indicate that 5% to 10% of all victims suffer varying degrees of permanent neurologic dysfunction, although some suggest that a higher percentage of patients will have long-term neurologic sequelae. Not surprisingly, those who sustain a cardiorespiratory arrest persisting to the time of presentation to the emergency room have a poor survival or a high incidence of neurologic sequelae. However, children who sustain what is reported as a "cardiorespiratory arrest" that responds to first-aid measures at the scene of the accident do not necessarily have a poor prognosis. In the late 1970s after a small experience of near-drowning incidents with a high percentage of victims with long-term neurologic sequelae, it was suggested that the incidence of neurologic dysfunction following near-drowning episodes could be lowered by aggressive attempts at cerebral salvage. This so-called *HYPER therapy* included barbiturate coma, controlled hyperventilation, diuretics, paralysis, intentional hypothermia, and adrenocortical steroids. The rationale for this therapy was to lower intracranial pressure (ICP), reduce cerebral edema, and lower cerebral oxygen demand. All of these measures were to prevent further (secondary) damage to the neurologic system. This mode of therapy presumes that further damage occurs after the initial anoxic insult, and that this further damage can be prevented by these measures.

Unfortunately, after more than two decades of experience with this mode of therapy, it is not clear that morbidity and mortality have changed appreciably. The largest study, performed by the group that originally advocated this therapy, reports a 7% incidence of neurologic morbidity. This is not appreciably different from multiple studies performed before the advent of this therapy. Additionally, although very high ICP is associated with a poor outcome, other studies suggest that normal ICP does not ensure neurologic recovery and that this therapy does not necessarily prevent elevation of ICP from occurring. Indeed, it appears that elevation of ICP is the result of brain injury, rather than the cause of it. Certainly, most authorities agree that if this therapy is indicated at all, it should be reserved for the most severely affected, in whom ICP is being monitored, and then only in an intensive care unit setting that is staffed, equipped, and experienced in handling this kind of patient. Even in such a setting, the portions of this therapy that are associated with significant morbidity should be reserved for victims whose ICP cannot be controlled by other more conventional means (e.g., hyperventilation, head elevation, osmotic diuretics).

The decision to admit the near-drowning victim to the hospital is somewhat controversial. Any victim with symptoms referable to the respiratory tract, an abnormal chest radiograph, or an abnormal arterial blood gas (i.e., signs or symptoms suggesting aspiration) should probably be admitted to the hospital, as pulmonary damage may not reach its peak for several hours after the accident. It is less clear whether patients who have suffered solely a loss of consciousness and present with normal neurologic function and no cardiopulmonary signs or symptoms require hospital admission

The most common cause of death related to scuba diving accidents is reported to be drowning. However, problems exist with data collection. Barotraumatic systemic gas embolism may, in fact, be the more common cause of death. The physiologic mechanism involved in this latter entity is related to Boyle's law, which states that in a closed system the product of pressure and volume remains constant at a given temperature ($P_1 V_1 = P_2 V_2$). If a submerged diver fills his or her lungs from a compressed gas source and then rises in the water column, that gas must expand because of the reduction in barometric pressure. If the egress of gas is blocked (i.e., a closed glottis), intrapulmonary blood vessels can rupture, allowing gas to enter the pulmonary venous circulation. Systemic embolism can then occur. The most common symptoms are referable to embolization of cerebral vessels. Sudden unconsciousness with subsequent aspiration can then occur. The expanding gas can also dissect through the interstitium of the lung to the hila, producing pneumomediastinum and subcutaneous emphysema at the base of the neck. Pneumothorax, rarely, can also occur. Treatment of barotrauma is supportive except if air embolism results. Recompression is then indicated. A variety of hematologic and biochemical abnormalities have been reported in victims of arterial gas embolism. However, other than recompression therapy, treatment is mainly supportive.

Pulmonary barotrauma with resultant cerebral air embolism is seen only in divers breathing from a compressed gas source. Swimmers who descend below the surface following an inspiration to total lung capacity will initially compress the gas in their chest. On surfacing, that gas will expand, but it does not expand to a volume greater than the initial total lung capacity and, therefore, does not cause barotrauma.

Decompression sickness, which also affects divers, rarely causes pulmonary problems. It presents with shortness of breath in less that 1% of cases. Most patients present with limb pain or spinal cord lesions, and also require recompression therapy. The pathophysiology is related to the absorption of an inert gas and a subsequent reduction in barometric pressure sufficient to generate a gas phase within the tissues of the body. The precise pathophysiologic mechanisms of the different forms and presentations of decompression sickness are still unclear. Prophylaxis for deep venous thrombosis in paralyzed divers is problematic as hemorrhage into the spinal cord secondary to bubble damage is thought to be a mechanism involved in the generation of paralytic symptoms. As a result, these patients must be monitored extremely carefully if heparin prophylaxis is not administered.

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87. AIR TRAVEL AND HIGH ALTITUDE MEDICINE

Timothy M. Clark

For most people, ascent to high altitude usually means a trip in the pressurized cabin of a commercial airliner. For others, it may be a swift ride on a ski lift or the more prolonged exposure of mountaineering. Although the fraction of inspired oxygen (F) is relatively constant, the partial pressure of inspired oxygen (P_{IO_2}) is directly related to barometric pressure, which decreases with elevation above sea level. For the person with lung disease, exposure to even moderate altitude with minor changes in P_{IO_2} can have important implications.

An ever-growing surge of both air travel and high altitude sojourns increases the need to understand normal adaptations to altitude, problems that can accompany air travel for patients with cardiopulmonary disease, and issues related to high-altitude exposure and the management and prevention of related complications.

Air Travel

Most commercial airplanes fly at altitudes between 22,000 ft (6706 m) and 44,000 ft (13,411 m). At these elevations, ambient barometric pressure falls from the normal 760 mm Hg at sea level to between 326 and 140 mm Hg, respectively. This causes a decrease in the P_{IO_2} [$P_{IO_2} = (P_B - P_{H2O}) * (F_{IO_2})$, where P_B = ambient barometric pressure and P_{H2O} = vapor pressure of water in the atmosphere]. The result is the equivalent of breathing between 8% and 3% fraction of inspired oxygen (F_{IO_2}). Partially recompressing the air makes commercial travel possible at those altitudes, resulting in a cabin pressure between 627 and 565 mm Hg—equivalent to an altitude of 6000 to 8000 ft (1829–2438 m) or an F_{IO_2} at sea level of 15% to 16%.

Most healthy persons tolerate such altitude exposure without difficulty. The known incidence of in-flight problems remains low. In-flight complaints were estimated at 260 per 8.7 million passengers during a 6-month period of incoming flights to Los Angeles. Also, 577 deaths per 245 million passengers were reported between 1977 and 1984 involving multiple international carriers. The Federal Aviation Administration mandates reporting of in-flight medical kit usage and found 2322 cases among an estimated 900 million passengers between 1986 and 1988. Most usage (85%) of medical kits was by physician passengers for complaints of chest pain, loss of consciousness, nausea and/or vomiting, and dyspnea.

Even with preflight screening, few problems can be anticipated. One study showed that of 1115 patients referred for screening, 1011 were cleared for travel and none had significant in-flight problems. The 104 who did not meet clearance criteria either had

unstable disease or violated airline policy such as necessary intravenous drug therapy. Regardless, recognizing the need for preflight evaluations and management requires some understanding of the risks involved for a variety of specific disease states.

Most patients with chronic obstructive pulmonary disease (COPD) can fly safely with little to no intervention. Nevertheless, considerable individual variation exists. Even the moderate altitudes achieved in commercial aircraft can produce changes in lung function. Forced vital capacity (FVC) falls at a simulated 8000 ft (2438 m) after 60 minutes in both normals and patients with severe COPD. Residual volume increases, whereas variable changes have been reported in airway resistance. Despite these changes, even patients with severe COPD often fly without difficulty. Only 18.2% of one cohort of 100 such patients flying for a median time of 3 hours over a 28-day period reported symptoms during flight. Complaints were primarily dyspnea, edema, wheezing, and cyanosis. Only two patients requested supplemental oxygen in flight and none required admission to a hospital. Other studies have shown similar results.

Pulmonary hypertension can also pose a significant—although not insurmountable—risk for air travel. Because hypoxia is known to induce increases in both pulmonary artery pressure (PAP) and pulmonary vascular resistance, patients should be evaluated carefully before travel. These patients may be limited by an inability to increase their cardiac output sufficiently to meet an increased demand, and even a mild increase in the level of hypoxia could mean a substantial increase in PAP.

Although some authors, including the Aerospace Medical Association, state that severe pulmonary hypertension is an absolute contraindication to flight, this may actually be a relative contraindication. Most agree that patients with mild to moderate pulmonary hypertension can travel with between 2 and 4 liters per minute (lpm) of supplemental oxygen, and continue all medications including anticoagulation. At the University of California, San Diego, where hundreds of patients with pulmonary hypertension fly on an annual basis, adverse outcomes have been rare as long as supplemental oxygen was used, even with mean PAP approaching systemic levels. A study of patients referred for transplant or pulmonary thromboendarterectomy with severe hypoxemia or pulmonary hypertension (mean PAP of at least 30 mm Hg), found that all but one arrived safely at destinations ranging 4 to 21 hours away from their origination. The one patient who died was mechanically ventilated with an FIO_2 of 80% and was hemodynamically unstable.

Other pulmonary disorders warrant special consideration. Exacerbation of asthma, which is one of the most common pulmonary problems reported during flight, can often be managed with the usual medications. Patients with severe asthma, such as those requiring frequent oral corticosteroids, may require a pulse of steroids before flight. The presence of a pneumothorax is an absolute contraindication to air travel; recommendations are to wait at least 2 to 3 weeks after resolution before flying. Any air in the chest cavity, such as that following thoracic surgery for any reason, should follow the same guidelines because the decreased pressure of even moderate altitude can cause expansion and a life-threatening tension pneumothorax.

Anticoagulation is also strongly encouraged for patients at risk for developing deep vein thrombosis (DVT) or pulmonary embolism. Commercial air travel is a well-known risk factor for DVT, comprising up to 10% of all cases. Extrinsic risk factors include immobility, dehydration, increased venous pressure from cramped seating, endothelial damage from seat edges, and hemoconcentration from fluid shifts to the interstitial space from decreased cabin pressure. Intrinsic risk factors that contribute to DVT from air travel include history of DVT or pulmonary embolism, postthrombotic syndromes, malignancy, pregnancy, and chronic venous insufficiency. High-risk patients should be treated with compression stockings and either warfarin or subcutaneous heparin before and after travel.

Finally, cardiac issues comprise the bulk of in-flight medical problems—and many pulmonary patients have limited cardiac reserve. Moderate hypobaric hypoxia, such as that occurring during flight, increases heart rate and cardiac output. Patients with a baseline hypoxemia or respiratory muscle weakness can decompensate as a result of acute exposure to moderate altitude. Similar to primary pulmonary problems, however, most cardiac disorders do not preclude flying in stable patients (in most cases, a brief waiting period of several weeks will likely suffice to demonstrate stability). For example, stable angina requires little if any change in management. For patients with

more severe angina (e.g., chest pain with minimal exertion), supplemental oxygen should be considered. Compensated congestive heart failure, even classes 3 and 4, follows the same guidelines. Per current recommendations, myocardial infarction requires 3 weeks of recovery and evidence of stable disease with exercise before travel, and complicated myocardial infarction requires 6 weeks before clearance.

Decompensated heart failure and unstable angina are considered absolute contraindications to air travel by the Aerospace Medical Association. Other cardiac disorders that may preclude travel by commercial airliner include (1) uncontrolled systemic hypertension; (2) less than 2 weeks following coronary artery bypass grafting, percutaneous transvenous coronary angioplasty, or cerebral vascular accident; (3) poorly controlled supraventricular or ventricular tachycardias; (4) Eisenmenger's syndrome; or (5) severe symptomatic valvular disease.

Supplemental oxygen can often circumvent most barriers to flight among patients with limited cardiopulmonary function. The ground level Pa_{O_2} has been the most useful predictor for which patients will require supplemental oxygen in flight, although the arterial Pa_{O_2} also suggests impaired gas exchange and probable need for oxygen evaluation. Oxygen should be considered for patients with a sea level Pa_{O_2} less than 70 mm Hg. For those with a Pa_{O_2} greater than 70 mm Hg, a number of preflight evaluations have been used to predict the oxygen requirement for the airborne patient with COPD. Some authors suggest simply adding 2 lpm of flow to baseline requirements to keep the Pa_{O_2} above 50 mm Hg. Others use more complicated prediction equations. Use of such equations requires considerable caution, because equations are derived from specific populations. More subjective issues such as cardiopulmonary reserve or muscle weakness are not included in the equations. Prediction equations also tend to overestimate Pa_{O_2} values for healthy controls. Below is one such equation that resulted in a high predictive value at moderate altitude.

$$Pa_{O_2}\ \text{alt} = 0.19(FEV_1 * Pa_{O_2}\ \text{grnd}) - 11.51[\ln(\text{max alt} - \text{grnd alt})]$$

Where Pa_{O_2} alt = Pa_{O_2} at expected altitude achieved, Pa_{O_2} grnd = Pa_{O_2} at baseline elevation, ln = natural log, max alt = maximum altitude achieved in meters, and grnd alt = baseline elevation in meters.

The hypoxia-altitude simulation test (HAST) can also assist in assessing oxygen demands for patients with a sea level Pa_{O_2} between 60 and 70 mm Hg. This test requires a pulmonary function laboratory and trained personnel and involves breathing hypoxic gas mixtures to simulate the altitude of a commercial aircraft (either 17.1% or 15.0% F_{IO_2}). The test has been validated by both comparing Pa_{O_2} values between normobaric hypoxia and hypobaric hypoxia, as well as comparing sea-level arterial blood gases with those in flight in a nonpressurized cabin. The test allows for subjective variation in hypoxic response, but does not account for any effects of exercise, acceleration, humidity, or temperature.

In summary, few medical problems occur during flight, and most can be circumvented with supplemental oxygen. The moderate altitude achieved in a pressurized cabin can affect lung function, but rarely significantly enough to produce clinically important sequelae. Patients with a Pa_{O_2} below 70 mm Hg should consider using supplemental oxygen, usually 2 lpm above baseline requirements. For persons with less clear indications for oxygen, the HAST or several prediction equations can serve as a guideline for oxygen therapy.

High Altitude Illness

Altitudes exceeding those typically experienced in pressurized cabins harbor a unique set of disorders that range from the benign to fatal. Fortunately, the more serious problems are less frequent. However, increasingly publicized accidents in remote locales reflect a surge of interest in high altitude adventure and altitude-related disorders. Although most of these problems occur in skiers, increasing numbers of people are adventuring into extreme environments at altitudes exceeding 14,000 ft (4267 m).

Ski resorts constitute the bulk of recreational destinations at high altitude; many are located above 9842 ft (3000 m) and people frequently arrive rapidly from low altitudes. Commercial activities occur at altitudes of 19,520 ft (5950 m) in Chile, and

individuals work at 13,779 ft (4200 m) at the Mauna Kea Observatory in Hawaii. Each year, some 6000 people climb Mt. Rainier at 14,408 ft (4392 m) and 800 climb Denali, the highest peak in North America at 20,320 ft (6193 m). Nearly 50% of all travelers to these altitudes will experience some symptoms of mountain sickness. Reports have noted that 66% of climbers on Mt. Rainier, 47% on Mount Everest, and 30% on Denali develop symptoms of altitude illness.

Factors contributing to the development of altitude-related illnesses include maximal altitude achieved, rate of ascent, level of exercise, viral illnesses, alcohol or sleep-enhancement drug consumption, and individual susceptibility. Other factors may include age and gender. Considerable evidence suggests that the incidence of mountain sickness increases substantially above approximately 10,000 ft (3000 m) and with rates of ascent greater than approximately 1000 ft (300 m) per day. A number of extrinsic factors can also contribute by way of lowering barometric pressure. Latitude, temperature, low-pressure storm systems, and winter season can result in lower barometric pressure than expected and, therefore, predispose to altitude-related illness.

Ascent to high altitude can produce a continuum of altitude-related illnesses including acute mountain sickness (AMS) and two uncommon, but potentially fatal, complications—high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE). A number of other altitude disorders can arise, but exceed the scope of this chapter. These include snow blindness, retinal hemorrhages, hypothermia, high-altitude flatus expulsion (a serious concern for climbers trapped in the closed confines of a tent during inclement weather), and problems associated with chronic exposure.

Acute adaptation to high altitude is similar to that discussed above at moderate altitude. At higher altitudes, FVC declines by approximately 4% at 15,000 ft (4572 m) and approximately 13% at 29,000 ft (8839 m), probably because of increases in interstitial edema. Other changes occurring as a result of acute exposure include increased minute ventilation and decreased lung compliance. Ventilation/perfusion matching becomes more homogeneous at rest but often worsens with exercise. Diffusion becomes a major determinant to adaptation, especially at extreme altitudes. Hemodynamically, cardiac output and cerebral blood flow increase, as does pulmonary vascular resistance from hypoxia-induced vasoconstriction. Although hemoglobin concentrations rise within 1 to 2 days from hemoconcentration, the role of oxygen affinity remains unclear (increases in 2,3-diphosphoglycerate may be offset by a respiratory alkalosis resulting from increased ventilation). Finally, acute hypobaric hypoxia results in a proportionally significant decrease in maximal oxygen consumption and exercise performance.

Acute mountain sickness is the most common altitude-related illness. Symptoms may appear immediately on arrival at altitude, or develop as many as 3 days after ascent, and usually resolve spontaneously. Among the chief complaints are headache, occurring in as many as 70% of visitors above 8000 ft (2438 m). Sleep-disordered breathing (e.g., Cheyne-Stokes respirations) and poor sleep are also common and may contribute to worsening disease. Other symptoms of AMS include nausea, vomiting, dyspnea, peripheral edema, malaise, anorexia, and fatigue. No specific laboratory markers of AMS exist, leaving the diagnosis to historical details in the appropriate setting.

The mechanism behind AMS is likely multifactorial. Chiefly, they are hypobaric hypoxia and individual response to the insult. Many, although not all, persons suffering from AMS have been found to have relatively low hypoxic ventilatory responses. In addition, many people experience an alteration in body fluid mechanics with retention and redistribution. Evidence also suggests increased cerebral blood flow and, possibly, capillary leak mediated by hypoxia-induced growth factors.

The self-limited nature of AMS usually requires only conservative management, even allowing for continued ascent after brief recovery periods. Treatment consists primarily of symptomatic measures such as acetaminophen or nonsteroidal anti-inflammatory drugs for headache or antiemetics (preferably prochloperazine because it increases hypoxic ventilatory response). For refractory or more severe cases, further ascent should be postponed and descent of at least 1000 ft (300 m) considered. Alternatively, sulfa-based acetazolamide has an established track record for both treatment and prevention. Most authors suggest either 250 mg, taken orally twice daily, or 500 mg of a long-acting preparation, taken orally every day, until symptoms resolve. Dexamethasone has also

been used successfully in treating AMS, usually at oral doses of 4 mg every 6 hours, although some suggest a loading dose of 8 mg. Failure to resolve after 1 to 2 days of conservative or medical management could indicate progression to HAPE or HACE and requires prompt attention, usually descent by whatever means possible, including helicopter evacuation as necessary.

Despite a considerably lower incidence of HAPE (~2% to 15%), the disorder carries potentially serious outcomes. As with AMS, HAPE typically occurs in young, fit men ascending rapidly to sleeping altitudes above 2500 m, more commonly after the second night at altitude. The pathogenesis, although not fully understood, likely involves a variety of changes in the pulmonary vascular system. Among them are hypoxia-induced vasoconstriction, hypertrophy of vascular muscle layers, altered pulmonary hemodynamics, and increased capillary permeability. These changes lead to extravasation of proteins, blood, and fluid from the pulmonary capillaries into interstitial tissue and alveolar units, causing a potentially cascading scenario of worsening inflammation and alveolar flooding.

Clinically, persons with HAPE invariably have symptoms of AMS, but will also have progressive dyspnea at rest or on exertion and, initially, a nonproductive cough that may progress to pink frothy sputum. Signs include increasing tachypnea, tachycardia, and cyanosis. Rales typically arise first in the right midaxillary line and spread diffusely with worsening disease, especially while sleeping. Chest x-ray studies reveal diffuse patchy infiltrates, with prominence of pulmonary arteries. Notably absent are Kerley B lines or other evidence of pulmonary venous congestion, because pulmonary capillary wedge pressures remain normal.

High altitude pulmonary edema is the most common cause of death from altitude-related illnesses and, therefore, requires immediate treatment. Descent remains the most important aspect of successful treatment of HAPE, with most authors recommending a descent of 2000 to 3000 ft (600–1000 m). Supplemental oxygen also plays a major role in treatment, if available. However, HAPE victims are often unable to descend secondary to their physical condition or poor weather. In these cases, the calcium-channel blocker nifedipine is suggested at oral doses of 20 mg every 6 hours for 1 to 2 days. Portable hyperbaric chambers (e.g., the Gamow® bag) can also simulate a descent of approximately 1476 ft (450 m), but are usually only found on large expeditions to very remote destinations.

High altitude cerebral edema, which occurs even more rarely than HAPE, may be a harbinger of death. Symptoms indicating HACE include worsening ataxia, changes in level of consciousness and coma, severe lassitude, seizures, cranial nerve palsies, retinal hemorrhages, cyanosis, and hallucinations superimposed on symptoms of AMS, HAPE, or both. Studies have shown elevated cerebral spinal fluid pressures (up to 300 mm Hg). Autopsies have also often revealed clinically indolent pulmonary edema. The disorder requires prompt recognition and immediate descent, if possible. In addition, dexamethasone and oxygen remain important adjuncts. Dexamethasone is often given in doses of 4 mg, intravenously, intramuscularly, or orally, followed by 4 mg every 6 hours. Portable hyperbaric chambers are also useful, when available.

In summary, increasing numbers of persons are traveling to high altitudes for a variety of reasons. Many of these persons will suffer symptoms of mild altitude illness, usually AMS. A few will experience HAPE or HACE, which require prompt attention and descent to prevent life-threatening progression.

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88. RADIATION-INDUCED LUNG DISEASE

Mark M. Fuster

Radiotherapy is used to treat various thoracic neoplasms. Frequently, lung tissue is injured in the process, as normal lung is a sensitive *innocent bystander* in the radiation field. Clinical pulmonary syndromes with radiographic infiltrates associated with exposure to thoracic radiation were first recognized in the early 1920s. The progres-

sion of *classic* radiation pneumonitis, characterized by an acute pneumonitis followed by chronic fibrotic changes, was described in that decade as well.

The pathogenesis of radiation pneumonitis stems from the ability of incident high-energy irradiation to excite electrons in lung tissue near or in the field of the target neoplasm. A number of free radicals and secondary reactive oxygen species resulting from these electrons cause intracellular protein denaturation, membrane disruption, and DNA alterations. Immediate effects of radiation on nongenetic macromolecules, including constituents of endothelial-cell membranes and type II cell lamellar bodies (containing surfactant), manifest as dose-related cytotoxicity. Animal models have shown that capillary endothelial disruption occurs within 1 week of radiotherapy. Most symptomatic pulmonary injury, however, results from damage to DNA, and occurs in specific cell types in relation to their respective rates of turnover. Bronchial epithelia are affected early (within days) postradiation, as they have a relatively rapid turnover rate. On the other hand, type I pneumocytes normally are nonproliferating cells; these are replaced by rapidly proliferating type II cells in response to radiation injury. In the first 2 to 3 months after radiation, the aforementioned changes result in the acute exudative phase of radiation pneumonitis. The nonspecific pathologic changes include endothelial cell swelling, variable capillary occlusion caused by microthrombi, as well as a fibrin-rich exudate (containing sloughed type I cells and acute inflammatory cells) in the interstitial or alveolar spaces. This is accompanied by hyalin-membrane change and decreased surfactant. The endothelial injury can persist for months, and can have profound influence on gas exchange and ventilation-perfusion matching.

Inflammatory cells in the acute phase of radiation pneumonitis induce a cytokine cascade, which ultimately mediates a host response characterized by fibrosis. Although radiographic fibrotic changes are typically not apparent until many months postradiation, collagen gene expression is augmented within 2 weeks of radiation exposure. The cytokine transforming growth factor-beta (TGF-β) appears to play an important role in fibrotic progression—particularly as a signaling mediator between macrophages, type II cells, and collagen-producing fibroblasts. The late, fibrotic phase of radiation pneumonitis develops 6 to 12 months following radiation, with the development of septal fibrosis, capillary loss, and obliteration of gas-exchanging units.

Several variables affect the degree of lung injury caused by radiation, the most important of which are related to the radiotherapy program and include dose, fractionation, and volume of lung irradiated. The relationship between injury and total delivered dose is steep, and results in a narrow therapeutic window. Fractionation allows a several times higher total dose to be delivered over any given volume with the same probability of lung injury, provided delivery occurs in installments—typically, daily over several weeks. For example, a single dose of 30 Gy can lead to severe clinical radiation pneumonitis and extensive lung fibrosis, whereas a similar dose given in 15 fractions may induce no clinical effects and minimal fibrotic change confined to the irradiated volume. This fractionation allows the therapist to augment total delivered dose. However, for any given fractionation schedule, the effect of increasing total dose on progression to radiation pneumonitis still remains. For instance, pneumonitis is virtually never reported following 20 Gy split into 2 Gy/d, whereas it is common once 35 Gy is delivered with the same fractionation schedule. Delivery of any given dose per schedule over a larger lung volume increases the probability of injury. (Also, whereas acute infiltrates are confined to the irradiated volume of lung, some nonclassic *out-of-field* changes can occur in the nonirradiated lung.) Radiation planning with computed tomography (CT) scanning techniques allows for optimization of radiation delivery to the minimal volume. Armstrong has demonstrated *3-D conformal radiotherapy* as a technique, which can reduce radiation outside the target volume significantly.

A number of other clinical risk factors can also play important roles in the development and progression of radiation pneumonitis. Following radiotherapy for lung cancer, some recently identified clinical risk factors include low performance status, smoking history, and comorbid lung disease with reduced baseline pulmonary function. Another concern specific to lung neoplasms is atelectasis (or even consolidated lung) encountered near the tumor, which appears to suffer more injury per unit of irradiated volume compared with normal adjacent lung. Drug-related variables also play an important role in radiotherapy for any type of thoracic neoplasm. Chemotherapy can

compound radiation toxicity, and clinical data strongly suggest avoidance of *concurrent* administration of adriamycin or actinomycin D with thoracic radiotherapy. Rather, *sequential* delivery of these drugs with radiation appears to be the safest option. Cisplatin, busulfan, bleomycin, and cyclophosphamide are other drugs that have been found to worsen radiation injury. The same drugs have also been implicated in a number of case reports of *recall pneumonitis*, whereby drug treatment weeks to months following radiation can precipitate an acute radiation pneumonitis-like syndrome within hours following drug delivery. Furthermore, rapid withdrawal of corticosteroids (often used to treat radiation pneumonitis) following radiotherapy can precipitate a flare of acute radiation pneumonitis. Interestingly, animal studies have shown that angiotensin-converting enzyme inhibitors may serve a protective role, although such drugs as yet have no clinical use in human radiation pneumonitis.

Historically, the incidence of radiation pneumonitis has been reported using either radiographic data alone, or any combination of clinical, radiographic, and pulmonary physiologic data from case series. In general, symptomatic radiation pneumonitis occurs less frequently (range of 1% to 34% in most series) than radiographic manifestations of radiation pneumonitis (e.g., >50% in several series for Hodgkin's disease, breast cancer, and mesothelioma). Symptomatic radiation pneumonitis, or at least postirradiation radiographic change, is especially prevalent following use of large direct radiation ports. On the other hand, radiographic changes have been reported with an incidence as low as 7% following tangential breast irradiation. Although most patients (>85% overall) have no clinical sequelae from use of modern radiation ports, equipment, and dosing techniques, most do sustain at least a small degree of eventual fibrotic change on the chest film. Thus, radiation fibrosis frequently occurs in the absence of clinically overt radiation pneumonitis.

The clinical features of radiation lung injury can be divided into two clinical syndromes: acute radiation pneumonitis and chronic radiation fibrosis. The onset of acute radiation pneumonitis is insidious, usually occurring 2 to 3 months after the completion of radiation therapy, although cases have been reported as early as 1 month after irradiation. The early onset of symptoms generally correlates with a more severe and protracted course. Symptoms secondary to tumor swelling or necrosis can occur within days, and symptoms reflecting bronchial epithelial alterations can occur within 1 week. The symptoms of acute radiation pneumonitis include cough, dyspnea, and occasional fever or pleuritic chest pain. The cough is typically paroxysmal and minimally productive, with occasional streaky hemoptysis. Dyspnea is usually exertional but can progress rapidly to resting shortness of breath. Physical examination is frequently unremarkable, but crackles, signs of consolidation, and pleural and pericardial rubs have been described. Skin changes usually occur over the irradiated field, but cutaneous manifestations do not correlate with the presence or severity of acute radiation pneumonitis. Patients receiving intraluminal endobronchial irradiation occasionally develop symptomatic radiation bronchitis and bronchial stenosis. The clinical course of acute radiation pneumonitis varies from days to weeks, with resolution common within 1 to 2 months. Rarely, rapid progression to respiratory failure and deaths have been noted. Radiographic improvement usually lags behind clinical improvement, with eventual fibrotic radiographic changes often remaining.

Radiation fibrosis develops to some degree in all patients who experience acute radiation pneumonitis, but it can appear radiographically in many that do not. The severity of radiation fibrosis correlates well with the severity of any preceding episode of acute pneumonitis. Most patients are asymptomatic or have minimal symptoms. On the other hand, in cases of a relatively large degree of pulmonary fibrosis, disease has progressed to severe exertional dyspnea and signs of cor pulmonale. In the absence of other underlying lung disease, symptoms tend to be mild when less than 25% of the lung parenchyma is involved. The physical findings of radiation fibrosis are those of interstitial fibrosis with volume loss; specific findings include inspiratory crackles, elevated hemidiaphragms, cyanosis, clubbing, and elevated venous pressure.

Laboratory findings include modest polymorphonuclear leukocytosis, elevated erythrocyte sedimentation rate, and hypoxemia with a widened alveolar-arterial oxygen gradient. The chest radiograph may show a ground-glass haze or indistinct bronchovesicular markings in the irradiated treatment area. Over time, the infiltrate may progress to nodularity; occasionally it becomes dense and confluent, containing air

bronchograms. Most radiographic findings are seen within the borders of the treatment area and have sharp margins correlating with the treatment port (*straight-edge effect*). This helps distinguish acute radiation pneumonitis from infection or lymphangitic spread of malignancy, the two most likely alternative entities in the differential diagnosis. Hilar or mediastinal lymphadenopathy, or areas of cavitation, should also prompt a search for such diagnoses. High resolution CT and magnetic resonance imaging are particularly useful in differentiating these processes. Recent research shows that perfusion abnormalities can precede roentgenographic or physiologic impairment. ^{99m}Technetium-labelled macroalbumin aggregates as well as 3-D single photon emission CT scanning are techniques that can detect such abnormalities in the patient who is symptomatic during the early postradiation period. Radiographic progression to fibrosis is characterized by a linear interstitial pattern, volume loss, and often pleural thickening. Pulmonary function tests show reduced lung volumes, decreased lung compliance, and increased work of breathing during the chronic phase of radiation pneumonitis. Decreased diffusing capacity of lung for carbon monoxide (DLCO) is a particularly sensitive finding during the 2- to 9-month period postradiation. If the volume of irradiated lung is large, gas exchange abnormalities, including hypercapnia, can be seen as well.

Several other complications attributed to radiation injury can also occur. Pleural effusions attributed to radiation pneumonitis are characteristically small, asymptomatic, and coincident with the onset of acute radiation pneumonitis. They usually resolve, but some effusions have been reported to persist for years. Recurrence or sudden increase in an effusion suggests malignancy or infection. Some less common complications include spontaneous pneumothorax, bronchial obstruction, rib fracture, pericardial effusion (rarely, constrictive pericarditis), superior vena cava syndrome, and tracheoesophageal fistula. Tracheoesophageal fistula leading to aspiration pneumonitis is usually seen in patients irradiated for carcinoma of the esophagus. Cystic and bronchiectatic changes can develop following large volume(s) of irradiation. Finally, involvement in the upper lung zones can mimic tuberculosis, with associated volume loss and occasional pleural thickening.

Other interesting *nonclassic* thoracic manifestations of radiation lung injury are seen. Radiographic changes have been reported outside the zone of lung irradiation with a variety of clinicopathologic patterns. One such pattern is a *migratory* form of bronchiolitis obliterans with organizing pneumonia (BOOP). Patients experience the onset of symptomatic migratory infiltrates months, or even years, following irradiation; histology of such infiltrates shows an organizing, granulation-tissue pattern consistent with BOOP. The infiltrates tend to respond well to systemic corticosteroids and do not appear to leave a significant degree of fibrosis after resolution. Another atypical response pattern is a generalized lymphocytic alveolitis involving both lungs, despite radiographic findings confined to the zone of initial irradiation. Morgan and others have shown that this out-of-field *hypersensitivity* type of response is characterized by significantly elevated bronchoalveolar lavage (BAL) lymphocyte counts from both lungs, a decreased vital capacity, and a decreased DLCO in patients who are symptomatic (compared with preirradiation values). Such responses have stimulated recent interest in a possible immunopotentiating effect of thoracic irradiation, although the molecular steps leading to the apparent T-lymphocyte activation are still under investigation. These responses may also serve to explain the wide spectrum of postradiation pulmonary symptom severity that sometimes appears out of proportion to that expected for the amount of lung volume originally irradiated.

Avoidance of radiation pneumonitis is a primary concern in planning treatment fields. Because curative treatment of most radiosensitive malignancies requires total doses in the range above pulmonary tolerance, the volume of tissue irradiated must be minimized and controlled closely. In patients with limited pulmonary function, symptomatic radiation pneumonitis can develop even when the volume of irradiated lung is limited. The patients at highest risk have a pretreatment FEV_1 less than 40% of predicted.

Therapy for acute radiation pneumonitis is primarily supportive. Patients who are asymptomatic with radiographic abnormalities do not require therapy. Usual measures for patients who are mildly to moderately symptomatic include the use of cough suppressants, antipyretics, analgesics, and supplemental oxygen when indicated for hypoxemia.

Corticosteroids appear to be most effective at the onset of clinically obvious radiation pneumonitis, and approximately 80% of patients respond with improvement in symptoms. Marked symptomatic relief may be observed with a decrease in cough, chest tightness, and fever along with coincident resolution of hypoxemia and radiographic abnormalities. However, a lack of response and continued deterioration despite corticosteroid therapy have been reported. Corticosteroids are usually given in doses of 60 mg/d of prednisone for several weeks, followed by a slow taper. Guidelines for dosing and tapering of corticosteroid therapy are not uniformly established, and no data show that prophylactic corticosteroids are effective in preventing radiation pneumonitis. Some experimental work suggests that nonsteroidal anti-inflammatory drugs may be used in the treatment of radiation pneumonitis. Prophylactic antibiotics are of no use and may predispose patients to aggressive, antibiotic-resistant organisms. Treatment of coincident infection should be guided by culture and other clinical information. No data exist to support the use of anticoagulants. Prevention of progression to radiation fibrosis is an area of active research, and no intervention in humans has been proved of benefit.

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89. DRUG-INDUCED LUNG DISEASE

Shazia M. Jamil

The overall incidence of drug-induced lung disease is unknown. Nearly 200 medications can cause some type of known adverse reaction within the respiratory system. However, almost any medication can cause an adverse pulmonary effect in a so-called *idiosyncratic reaction* that may have not been reported. It is important for physicians to be aware of all medications that a patient is taking, including over-the-counter preparations, vitamins, supplements, ophthalmic solutions, illicit drugs, topically applied creams; and ointments (vaginal). Patients should also be asked about medications used intermittently. Reviewing medical records is particularly important in obtaining information about medication identify, doses, and duration of treatment.

The clinical presentation, chest x-ray findings, laboratory studies, pulmonary function studies, nuclear medicine studies, and even lung biopsies in patients with drug-induced lung disease are usually nonspecific. However, these can be helpful in supporting the diagnosis or in limiting the differential diagnostic considerations. In the absence of a simple confirmatory test, discontinuation of the putative drug is the first step in both diagnosis and treatment. Unfortunately, the patient's response to discontinuing the drug may not be immediate, and the physiologic and pathologic changes in some cases may be irreversible. Rechallenge with the same medication is rarely indicated to confirm the diagnosis.

Drug-induced lung disease can be approached by dividing the known adverse reactions into pathophysiologic and clinical syndromes (Table 89.1). In this discussion, each pathophysiologic syndrome is reviewed briefly and includes a description of only the most common and clinically significant drugs. Tables 89.2 to 89.5 list some of the more important syndromes, along with the most commonly implicated drugs. Some drugs cause a variety of pulmonary disorders and are listed under different categories.

Aspiration of mineral oil laxatives or an oily eye lubricant is often asymptomatic but typically presents as a chronic infiltrate or a nodule in the dependent areas of the lung. Occasionally, a computed tomography (CT) scan may show a fat density within the lesion. Biopsy demonstration of oil within the lung parenchyma is confirmatory.

Angioedema is an uncommon fatal complication of angiotensin-converting enzyme inhibitors, and is seen more commonly in obese individuals with a past history of intubation or head and neck surgery. Angioedema is also reported with the use of losartan and taxol.

Alveolar hemorrhage in the lung has been reported with anticoagulant therapy; when this occurs, the possibility of an underlying intrapulmonary lesion should be considered. D-Penicillamine may rarely cause a Goodpasture's-like pulmonary-renal syn-

Table 89.1. Pathophysiologic and clinical syndromes induced by drugs

Aspiration	Lupuslike syndrome
Angioedema	Mediastinal lipomatosis
Alveolar hemorrhage	Obliterative bronchiolitis
Bronchiolitis obliterans with organizing pneumonia	Pulmonary hypertension
Bronchospasm	Pleural disease
Calcification	Pneumothorax
Cough	Pulmonary nodules
Chest pain	Pulmonary edema, noncardiogenic
Churg–Strauss syndrome	Pulmonary infiltrates with eosinophilia
Granulomatous disease	Pulmonary thromboembolism
Hilar adenopathy	Pulmonary septic emboli
Hypoventilation	Pulmonary veno-occlusive disease
Hypersensitivity	Respiratory dyskinesia
Interstitial disease	Vasculitis

drome with alveolar hemorrhage in patients who have received the medication for a long period of time. The presentation is acute, with dyspnea, hemoptysis, and hematuria; however, unlike Goodpasture's syndrome, immunofluorescence of biopsy tissue fails to demonstrate linear deposition of immunoglobulin. Plasmapheresis has been used successfully in three of seven reported survivors. Some cephalosporin antibiotics are reported to cause alveolar hemorrhage by hypoprothrombinemia that is related to their side chain *N*-methylthiotrazole and methylthiotetrazole and appear to be a consequence of inhibition of hepatic vitamin K epoxidereductase enzyme. Concurrent therapy with vitamin K, especially in patients receiving parenteral nutrition, helps to prevent this complication. Diffuse alveolar hemorrhage has also been reported following smoking of cocaine, use of nitrofurantoin and thrombolytics, and, more recently, after multiple intravenous doses of amiodarone.

Bronchospasm can be precipitated by oral, intravenous, or ophthalmic administration of nonselective β-adrenergic antagonists. Timolol ophthalmic solution has been reported to be responsible for more than 100 deaths because of aggravation of asthma or emphysema. Bronchospasm has also been reported with atenolol, which is relatively β_1-selective; therefore, this drug should be avoided if possible in patients with obstructive lung disease. Inhaled ipratropium bromide is the drug of choice in treating the bronchospasm induced by beta blockade. Sulfiting agents used as preservatives can provoke bronchospasm in susceptible individuals. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are the most common cause of drug-induced bronchospasm, occurring with a reported incidence of 5% to 10% in asthmatics. These patients may have aspirin-sensitive asthma, a triad of aspirin sensitivity, nasal polyposis, and asthma. Bronchospasm generally develops within minutes of ingestion. Approximately 8% of asthmatic admissions in the intensive care unit may be precipitated by an inadvertent aspirin or other NSAID usage, as more than 200 aspirin-containing, over-the-counter products are available. These agents should be avoided in all patients with moderate to severe persistent asthma. Inert materials in corticosteroid and cromolyn preparations can also cause paradoxical bronchospasm in asthmatics. Drug-induced histamine release from mast cells has been implicated in bronchospasm occurring with morphine and muscle relaxants (D-tubocurarine and atracurium). Slower administration of these intravenous medications or alternative drugs (e.g., fentanyl and vecuronium) should be considered. Bronchospasm can also occur with contrast media injection, cholinesterase inhibitors, aerosolized pentamidine, and protamine.

Bronchiolitis obliterans with organizing pneumonia secondary to drugs is histologically and radiologically indistinguishable from non–drug-induced disease. In the case of gold and penicillamine, the separation of drug-induced effects from the underlying rheumatic disease may not be possible.

Calcification is a rare complication reported following prolonged treatment with busulfan. Hypervitaminosis D or inorganic phosphorus administration to a patient with hypercalcemia can cause metastatic calcification within the lung. Intravenous calcium gluconate has been reported to cause calcifications both within the lung parenchyma and over the surface of the lung. Technetium 99m diphosphonate scans and dual-energy digital chest radiography may help to confirm the diagnosis.

Cough is a recognized complication of all of the angiotensin-converting enzyme inhibitors; hence, switching from one to another does not help. This cough has been linked to an accumulation of bradykinin or tachykinins in the airways with consequent stimulation of vagal afferents. It can take several weeks for cough to resolve after drug withdrawal. Concomitant use of inhaled cromolyn appears to minimize the cough in some patients. Methotrexate-induced pneumonitis commonly produces a dry cough; a productive cough is uncommon and warrants search for another cause because patients on methotrexate are susceptible to opportunistic infections.

Chest pain (acute) occurring during bleomycin infusion has been reported in approximately 3% of patients. Chest pain, the single most common presenting symptom of patients abusing cocaine, could be caused by bronchial irritation, valsalva maneuver during inhalation, coronary artery spasm, or myocardial infarction. Acute chest pain syndrome has also been reported with methotrexate therapy.

Churg–Strauss syndrome has been associated with zafirlukast, a leukotriene receptor antagonist used by asthmatics. More than 40 cases have been reported to the manufacturer. It is unclear whether this is secondary to increased case finding in patients receiving a new drug, a reduction in corticosteroid doses, or an idiosyncratic reaction.

Granuloma formation is described with bacillus Calmette–Guerin, methotrexate, nitrosureas, fluoxetine, oil aspiration, and talc. Talc granulomatosis is reported to occur in intravenous drug abusers mixing illicit drugs with talc (magnesium silicate) containing fillers. Talc is identified as strongly birefringent crystals within the granuloma on biopsy.

Hilar adenopathy occurs rarely in association with phenytoin or hydantoin analog (mephenytoin and ethotoin) therapy. Hydantoin-related adenopathy is usually seen 1 to 4 months after initiating therapy and regresses within 1 to 2 weeks after withdrawal of the medication. Hilar adenopathy is a common feature of methotrexate-induced hypersensitivity pneumonitis.

Hypersensitivity reactions are characterized by the acute onset of fever, nonproductive cough, dyspnea, urticaria, arthralgias, and peripheral eosinophilia. Pleuritic chest pains, pulmonary infiltrates, and pleural effusions may be present. A large number of drugs have been implicated, most notably ampicillin, azothioprine, phenytoin, sulfasalazine, and hydrochlorthiazide. The reactions are not dose related. The mortality rate is less than 1% with discontinuation of the offending agent. A short course of corticosteroids may promote rapid improvement.

Hypoventilation can be caused by central nervous system (CNS) depression from narcotics, sedatives, anxiolytics or psychotropic medications, and by neuromuscular blockade. The degree of neuromuscular blockade can be tested with a nerve stimulator or, in a cooperative patient, by asking the patient to elevate the head for 5 seconds or more. Neuromuscular blockade is also seen with aminoglycosides, macrolides, and, rarely, calcium channel blockers.

Interstitial lung disease (acute interstitial pneumonitis, chronic pneumonitis, and fibrosis) is a common manifestation of drug-induced lung disease (Table 89.2). Diagnosis in an immunocompromised host is challenging because a similar picture can develop with recurrence of underlying disease, metastasis, and opportunistic infections. Drug-induced lung disease secondary to use of chemotherapeutic agents is almost always associated with fever. Bleomycin can cause pulmonary disease in 10% of patients, of whom 10% die of pulmonary sequelae. Clinically, acute pneumonitis, chronic pneumonitis, and fibrosis are well described. The risk factors for developing lung disease from bleomycin are a total dose of more than 400 to 450 mg, increased age, higher inspired oxygen concentrations, radiation therapy, and multidrug cytotoxic regimens. Lung volumes and diffusing capacity (DLCO) should be measured on a regular basis during treatment. Treatment consists of discontinuing the drug; dramatic responses with steroids have been noted. Busulfan lung toxicity is usually seen after a total dose of 2 g. Busulfan

Table 89.2. Chronic interstitial infiltrates

Amiodarone	Mecamylamine
Bleomycin	Melphalan
Busulfan	Methotrexate
Chlorambucil	Methysergide
Cyclophosphamide	Mitomycin
Gold salts	Nitrofurantoin
Hexamethonium	Sulfasalazine
Interleukin-2	

pulmonary fibrosis often progresses after discontinuation of treatment, does not respond to corticosteroids, and is associated with high mortality. Carmustine (BiCNU) lung toxicity is reported with cumulative doses greater than 1000 mg/m^2. Both carmustine and cyclophosphamide can cause pulmonary fibrosis years after discontinuation.

Amiodarone is a potent phospholipase inhibitor that results in intense cellular phospholipid accumulation. Incidence of drug-induced lung disease is 10% to 15%; of these, the mortality rate is reported to be 10% to 20%. Both chronic pneumonitis and fibrosis occur. Known risk factors for amiodarone-induced lung disease are a high maintenance dose of more than 400 mg/d and, possibly, pre-existing pulmonary disease. Proposed mechanisms include phopholipidosis, altered calcium ion regulation, generation of oxygen species, formation of an amiodarone aryl radical, and perturbation of cellular energy production. Diagnosis can be difficult, even with lung biopsy, as phopholipid-laden lamellar body inclusions in macrophages are seen commonly in all patients on treatment without lung toxicity. CT scan can be helpful if it shows areas of high attenuation, owing to amiodarone being an iodinated compound. The current approach is to change the antiarrhythmic therapy, if possible, or to reduce the dose and treat with corticosteroids. However, because of tissue accumulation, the elimination half-life after discontinuation is 30 to 60 days, requiring a prolonged treatment with corticosteroids.

Gold-induced lung disease is difficult to diagnose in patients with rheumatoid arthritis. Criteria favoring interstitial lung disease from gold rather than rheumatoid arthritis include female gender, fever, peripheral eosinophilia, absence of clubbing and subcutaneous nodules, skin rash, liver dysfunction, bronchioalveolar lavage lymphocytosis with $CD4^+$:$CD8^+$ ratio of less than 1.0, pleural involvement (rarely), and nonbasilar predominance of lung infiltrates. Therapy includes discontinuation of the drug and treatment with corticosteroids; this has been reported to cause complete clinical remission in 71% of patients.

Methotrexate, both in high doses used in the treatment of malignancy and low doses used in treatment of rheumatoid arthritis, is known to cause severe pulmonary toxicity. Both hypersensitivity and non-hypersensitivity pneumonitis and pulmonary fibrosis are described. Low-dose methotrexate is also a risk factor for opportunistic infection leading to pneumonia, *Pneumocystis carinii* being one of the most common. In methotrexate pneumonitis, chest radiographs reveal bilateral, diffuse interstitial and alveolar infiltrates. Bronchioalveolar lavage usually shows a predominant helper T-cell lymphocytosis and lung biopsy reveals a lymphocytic interstitial pneumonitis, bronchiolitis, and giant-cell formation. Treatment is discontinuation of the drug; high-dose corticosteroids are indicated in severe cases. Acute nitrofurantoin pneumonitis occurs a few hours to days after initiation of treatment. The chest radiograph usually reveals an asymmetric or unilateral alveolar or interstitial infiltrate; hence, this condition is often confused with bacterial pneumonia. Chronic nitrofurantoin use is the classic example of noncytotoxic, drug-induced pulmonary fibrosis, which is indistinguishable from idiopathic pulmonary fibrosis. Reversibility of lung disease following discontinuing the drug is almost always seen, although one half of cases may require addition of corticosteroids.

Lupuslike syndrome (Table 89.3) with lung involvement occurs most commonly with procainamide, hydralazine, phenytoin, penicillamine, and isoniazid use. Fever, pleuritis, pleural effusions, and arthralgias can occur. Symptoms can occur as early as 1 month or as late as 12 years from the start of treatment. Renal and CNS involvement are rare.

Table 89.3. Drugs associated with a lupus-like syndrome

Chlorpromazine	Trimethadione
Quinidine	Ethosuximide
Methyldopa	Gold salts
Nitrofurantoin	Griseofulvin
Phenytoin	Hydralazine
Para-aminosalicylic acid	Isoniazid
Penicillamine	Lithium carbonate
Penicillin	Oral contraceptives
Phenothiazine	Mephenytoin
Phenylbutazone	Propylthiouracil
Reserpine	Practolol
Streptomycin	Prazosin
Sulfonamides	Primidone
Tetracycline	Procainamide
Thiazide diuretics	

Antinuclear antibody (ANA) is usually positive; antihistone antibodies are positive, whereas anti-dsDNA antibody is negative, and complement levels are normal. ANA positivity can persist for several months, but the symptoms usually resolve within 2 months of discontinuing the drug. Steroids may be beneficial.

Mediastinal lipomatosis is an unusual reaction to chronic corticosteroid intake. Fat is deposited in the mediastinum, mimicking a mediastinal tumor; hence, its importance in the differential diagnosis of mediastinal mass. A CT scan is helpful in detecting fat rather than tissue density throughout the mediastinum. As this almost never compromises vital structures, tapering of steroids is not necessary.

Obliterative bronchiolitis without parenchymal involvement has been reported with gold, penicillamine, and amphotericin B.

Pulmonary hypertension has been reported with intravenous and nasal cocaine abuse. Drug-related thrombosis, particulate embolization (talc and starch granules), and talc granulomatosis occurring around pulmonary arterioles, can cause pulmonary hypertension. Funduscopic examination reveals a characteristic white, glistening, refractile particle (talc) within the small vessels near the macula in approximately half of these patients. Appetite suppressants fenfluramine and dexfenfluramine have recently resulted in an outbreak of pulmonary hypertension (PHT), the pathology of which is reminiscent of primary pulmonary hypertension. The use of fenfluramine-related anorexigens for more than 3 months increases the risk of developing PHT about 23 times. The pathogenesis is not entirely clear, but hypotheses have implicated serotonin and direct vasoconstrictor effects of amphetaminelike substances contained in anorexic agents. Recent evidence suggests that persons with relative nitric oxide deficiency may be predisposed to develop PHT. This is a major public health problem because it is estimated that 18,000,000 prescriptions of fenfluramine were filled in the United States in 1996 alone. PHT has also been reported with chronic methamphetamine use. Protamine can cause acute onset pulmonary vasoconstriction, leading to pulmonary hypertension; this is seen most commonly during heparin reversal following cardiopulmonary bypass surgery.

Pleural effusion, pleural thickening, and pleuritis can occur because of a drug-induced serositis, cardiac decompensation with associated pulmonary edema, constrictive pericarditis, pulmonary emboli, or vasculitis. The esophageal variceal sclerotherapeutic agents (sodium morrhuate and absolute alcohol) are common causes of pleural effusions. Pleural effusion is usually right sided and spontaneously resolves within 7 days. The proposed mechanism is transmediastinal inflammation from the esophagus to the mediastinal pleura and pleural space. Drug-induced lupus pleural effusions are exudative, with nucleated cell counts of 200 to 15,000/μl, and may demonstrate a pleural fluid:ANA ratio greater than 1.0; however, the presence of lupus erythematosus cells is the only diagnostic finding. Drug-induced lupus pleuritis improves rapidly after dis-

continuing the drug, whereas NSAIDs or a short course of corticosteroids may be beneficial in patients with severe or prolonged symptoms. Pleural fluid eosinophilia (>10% of nucleated cells) is seen with nitofurantoin, dantrolene, valproic acid, propylthiouracil, and isotretinoin.

Pneumothorax and pneumomediastinum have been well documented in crack cocaine abusers as a result of attempting to increase the alveolar-capillary absorption with a valsalva maneuver. Nitrorsureas are also known to cause pneumothorax.

Pulmonary infiltrates with eosinophilia (PIE) syndrome (Table 89.4) is attributed to many drugs. It is similar to Löffler's syndrome, although frequently more severe. Cough and dyspnea, with or without fever, can begin abruptly or insidiously after institution of the drug. Chest roentgenograms typically reveal unilateral patchy alveolar infiltrates, which are frequently migratory. Peripheral eosinophilia (4% to 80%) often peaks as the infiltrate wanes. Recovery occurs rapidly after discontinuation of the offending drug. Steroids may hasten the recovery.

Pulmonary nodules have been reported with use of amiodarone, bleomycin, and mineral oil. In patients with malignancy being treated with bleomycin such a finding may pose a clinical dilemma as it mimics metastases and can warrant early biopsy and pathologic diagnosis. Amiodarone can cause mass lesions with cavitations.

Pulmonary edema (Table 89.5), both cardiogenic and noncardiogenic, can be induced by a number of drugs. Opiates, including heroin, methadone, codeine, buprenorphine, and the narcotic antagonist, naloxone, both in therapeutic doses and in overdose, can cause noncardiogenic pulmonary edema. Patients typically present with stupor, depressed respiration, and miotic pupils. Prognosis is excellent with supportive care. Aspirin-induced noncardiogenic pulmonary edema almost always occurs with serum levels above 40 mg/dl. Clinical presentation includes acute dyspnea, fever, obtundation, a high anion gap metabolic acidosis, and respiratory alkalosis. The prognosis is good with supportive treatment, and early detection is important to prevent long-term sequelae of salicylate ingestion. Tocolytics, namely terbutaline, albuterol, and ritodrine, have also been reported to cause pulmonary edema. Tocolytic agents are started to halt premature labor and produce vasodilation and increased intravascular volume. It is proposed that on discontinuation and reversal of vasodilation, the lungs may be subjected to a large intravascular volume leading to pulmonary edema. This could be multifactorial as these patients are often also started on intravenous fluids and corticosteroid therapy to accelerate fetal lung maturation. Transfusion-related acute lung injury is a pulmonary leukoagglutinin reaction to sensitized lymphocytes from multiparous female donors. Acute respiratory distress syndrome (ARDS) occurs within minutes to a few hours of blood transfusion and may be associated with fever, hypotension, and rash. Treatment is supportive and recovery is dramatic—within 48 hours to a week. The donor and recipient need to be tested for leukoagglutinating antibodies to confirm the diagnosis. Finally, 10% to 25% of patients receiving amiodarone may develop ARDS in the postoperative period, usually after angiography and cardiothoracic surgery; typically, this occurs 18 to 72 hours later. The mechanism is unknown and treatment is supportive.

Septic pulmonary emboli are seen most commonly in intravenous drug users as a consequence of septic thrombophlebitis and right-sided endocarditis caused by contaminated needles.

Table 89.4. Drugs associated with PIE syndrome

Acetylsalicylic acid	Methotrexate
Amiodarone	Methylphenidate
Aurothioglucose	Nitrofurantoin
Chlorpropamide	Para-aminosalicylic acid
Disodium cromoglycate	Penicillin
Imipramine	Pituitary snuff
Isoniazid	Procarbazine
Mephenesin carbonate	Sulfonamides

PIE, pulmonary infiltrates with eosinophilia.

Table 89.5. Drugs associated with noncardiogenic pulmonary edema

Amitriptyline	Nitrofurantoin
Aspirin	Oxyphenbutazone
Chlordiazepoxide	Penicillamine
Colchicine	Phenylbutazone
Dextran	Phenytoin
Epinephrine	Protamine sulfate
Ethchlorvynol	Sodium morrhuate
Heroin	Sulfonamides
Hydrochlorothiazide	Tocainide
Interleukin-2	Tocolytics
Lidocaine	Transfusion-related injury
Metaraminol	Trimethoprim–sulfamethoxazole
Methadone	

Pulmonary thromboembolism and deep venous thrombosis occur with increased frequency in patients taking oral contraceptives. The risk is greatest during the first year and is probably associated with other risk factors.

Pulmonary veno-occlusive disease has been reported with carmustin (BiCNU), bleomycin, mitomycin, cyclophosphamide, and zinostatin.

Respiratory dyskinesia is an irregular tachypneic pattern of breathing caused by respiratory muscle involvement by the tardive dyskinesia associated with neuroleptic medications. Interestingly, this can occur in the absence of usual dyskinetic movements of tongue, face, and neck. Presentation includes an irregular breathing pattern, tachypnea, and dyspnea that worsens with anxiety and pain. Pulmonary function tests are normal; arterial blood gases show a high Pa_{O_2} and a low Pa_{CO_2} and, hence, is usually mistaken for psychogenic hyperventilation. Unfortunately, symptoms may persist after discontinuation of the offending drug.

Pulmonary vasculitis, usually accompanying a systemic vasculitis, has been reported with the use of sulfonamides, penicillin, thiouracil, hydralazine, phenylbutazone, quinidine, promazine, and the hydantoins. Illicit use of intravenous drugs contaminated with insoluble particulates can induce a localized vasculitis when trapped within the lung. A hypersensitivity angiitis can occur from serum sickness (antivenom) or secondary to a drug-induced small vasculitis.

Rare syndromes of drug-induced pulmonary disease include *lymphoma* from low-dose methotrexate; *alveolar proteinosis* from busulfan; *sarcoidosis* with nitrosureas; *microangiopathic hemolytic anemia, renal failure*, and *noncardiogenic pulmonary edema* from mitomycin-C; pulmonary manifestations of *eosinophilic myalgia syndrome* with L-tryptophan ingestion; and noncardiogenic pulmonary edema after intrathecal methotrexate administration.

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90. TOBACCO CONTROL

David M. Burns

Tobacco use in the Americas preceded the arrival of Columbus to the New World, but the vast majority of tobacco was used as chewing tobacco, snuff, pipes, and cigars until the 20th Century. Invention of machines that could manufacture cigarettes and the development of mass marketing techniques led to a rapid rise in cigarette smoking, beginning in 1913. The more acidic pH of cigarette tobacco smoke results in less absorption of the active ingredient, nicotine, across the oral mucosa. This lower oral absorption requires inhalation into the larger absorptive surface of the lung for the smoker to get the desired dose of nicotine. The increased deposition, absorption, and retention in the lung of toxic and carcinogenic constituents from cigarette smoke has produced an epidemic of cancer, heart disease, and chronic lung disease during the middle and latter parts of the 20th Century.

Cigarette smoking causes cancer of the lung, oral cavity, esophagus, larynx, pancreas, kidney, and urinary bladder as well as coronary artery disease, cerebrovascular disease, aortic aneurysm, peripheral vascular disease, and chronic obstructive pulmonary disease. Women who smoke are also at increased risk of vascular disease if they use oral contraceptives, and they have higher fetal and maternal complications of pregnancy if they smoke during the last 6 months of pregnancy.

Prevention of smoking initiation is an important public health goal, but smoking cessation is the principal means by which a current cigarette smoker can alter his or her risk of disease. Prevention of initiation among adolescents can reduce smoking prevalence, but adolescents contribute little to rates of smoking-related illness until they have been smoking for 30 years or more.

Since the 1960s, tobacco control strategies have gradually transitioned from a focus exclusively on the individual smoker toward understanding the role in promoting and enhancing cessation played by the environment within which the smoker smokes. Efforts to educate the smoker and clinic-based cessation assistance have been supplemented by efforts to change community norms, increase the cost of cigarettes, restrict where smoking is allowed, and provide societal-based persistent and inescapable messages to quit coupled with support for cessation.

Changes in public policies on tobacco can affect large numbers of individuals at minimal cost. Changes in the price of cigarettes have repeatedly been linked with a reduction in total and per capita cigarette consumption; most studies have shown a relatively consistent effect of a 4% decline in consumption for each 10% increase in price. This relationship has been revalidated with the fall in cigarette consumption nationally following the $0.45 increase in cost of cigarettes that resulted from the recent settlement of lawsuits by state Attorney Generals to recover tobacco-related Medicaid expenditures, and by the even steeper decline that occurred in California when a $0.50 increase in cigarette tax was added to the $0.45 national price increase. More limited data are available for cessation, but it appears that an increase in the cost of cigarettes can also influence both short-term cessation attempts and long-term cessation success.

A dramatic increase is seen in the fraction of the working population protected by total bans on smoking in the workplace, increasing from 3% in 1986 to 64% in 1996. Multiple workplace observations have demonstrated that instituting a change in workplace smoking restrictions is accompanied by an increase in cessation attempts and a reduction in number of cigarettes smoked per day. Once restrictions on smoking in the workplace have been successfully implemented, they continue to have an effect. Working in a smoke-free workplace reduces the number of cigarettes smoked per day and increases the success rate of smokers attempting to quit.

The healthcare system has long been recognized as a logical and potentially productive means of reaching smokers with a cessation message and promoting their successful cessation. Approximately 70% of smokers see a physician each year, creating the potential to reach large numbers of smokers with a cessation message. The fraction of patients who report having been advised to quit in the last year by their physician

remains too low, but it has been increasing over time and now exceeds 50% of smokers. The US Food and Drug Administration has approved a variety of pharmacologic approaches to smoking cessation over the last two decades including nicotine replacement therapy with gum, patches, nasal and oral inhalers; clonidine; and bupropion. The nicotine patch and gum have been approved for over-the-counter sale since 1996.

Both physician advice and pharmacologic treatment have substantive effects on long-term successful smoking cessation, which has been demonstrated in multiple controlled clinical trials. In their office, physicians should take a smoking history, motivate the smoker to quit, negotiate a quit date, follow-up the quit attempt, and attempt to link the smoker to additional cessation assistance. When physicians provide this type of intervention, they can double the rate of long-term successful cessation in their patients. In addition, physician encouragement can also double the likelihood that a patient will participate in more structured cessation assistance such as a smoking clinic. Once these interventions move beyond the controlled investigational setting with careful attention to details of the intervention protocol and are used in isolation without the structure and support provided by a clinical trial, it is likely that they will have less impact on the smoker.

The gap between the effect achieved in clinical trials and population-based data defines the potential that can be achieved if these modalities are delivered in a more comprehensive, organized manner that is integrated with other available cessation resources. If physician advice can achieve the effectiveness demonstrated in clinical trials, it could result in as many as 750,000 additional quits among the 35 million smokers who visit physicians each year. If the success rate of pharmacologic interventions matched that in clinical trials, as many as 500,000 additional quits could be achieved each year; and an even greater number could be expected if more smokers who are trying to quit could be persuaded to use pharmacologic methods.

Improving the effectiveness of these interventions requires focusing resources on enhancing the capacity of other tobacco control structures to support these pharmacologic and physician-based interventions. This can be accomplished by reducing barriers to access (particularly cost) and by linking them with other existing tobacco control interventions. For example, linking physician advice with telephone hotline counseling, providing information on how to effectively use over-the-counter medications at community cessation events, and encouraging healthcare systems to view cessation as a population-based intervention delivered across all interactions with the system rather than initiated exclusively by physicians could enhance effectiveness. To obtain maximal benefit, we need to integrate them into healthcare delivery systems, link them to community cessation resources, and create an environment that encourages access. When this is done, dramatic improvements in population-based rates of cessation are possible.

Two common components of most comprehensive tobacco control programs are mass media and self-help materials. They share the ability to reach large numbers of individuals at relatively low cost. However, they also share the misconception that they are autonomous interventions whereby cessation goals are achieved simply by delivering the self-help materials to the smoker or having the smoker exposed to the media message. It is clear that both of these tobacco control channels are just that, channels. They are methods by which other tobacco control interventions can be facilitated, reinforced, and publicized and by which agendas can be set; however, in isolation, without integration into a more comprehensive approach, they have little effect.

Changing the environment in which the smoker lives and smokes to provide persistent and inescapable messages to quit, coupled with support for cessation, has been a goal of most comprehensive tobacco control approaches, but accomplishing this goal has been problematic. Approaches that attempted to activate communities to promote smoking cessation (e.g., the National Cancer Institute COMMIT trial) have yielded modest results and have not reached heavy smokers. The limited impact of these community activation approaches may result from underestimating the length of time required to sufficiently alter the community in ways that can have an impact on the smoker. The lack of an effect may also result from the decision to intervene at the level of small communities, rather than at the state level, where more powerful policy options (e.g., tax increases) are possible.

Considerable data support the effectiveness of telephone counseling services in promoting long-term successful cessation. Several newer approaches to individualized counseling have recently been developed that offer the potential to provide assistance to the general population of smokers. Computer-based interactive software can tailor the intervention and counseling provided to the individual smoker. The potential to provide this kind of tailored intervention over the Internet, in public locations where smokers have access, on home computers, or in hand-held devices could overcome some of the traditional resistance of smokers to the more intensive, but more effective, smoking cessation interventions.

Community and local activity are the foundations of comprehensive tobacco control programs. However, because they are so broad based, it is difficult to independently quantify them as interventions and to demonstrate their association with individual or population-based cessation activity and success. Nevertheless, the fact that we have limited tools to accurately measure community interventions does not necessarily mean that community programs have limited effects.

Current models of smoking behavior postulate that smokers cycle through stages where they are disinterested in cessation, contemplate quitting, make a quit attempt, and are either successful or relapse back to smoking. Smoking relapse can be followed by a period of disinterest in cessation or the smoker may think about making an additional cessation attempt. Individual components of a comprehensive tobacco control program may effect the process of cessation at different stages. For example, public information campaigns can help smokers think about the need to quit, physician advice may trigger a cessation attempt, and working in a smoke-free environment may facilitate cessation once the attempt is made. Public information about the risks of smoking, negative images of the smoker, and physician warnings about risks can all convert a smoker who is not interested in quitting into one who is considering a cessation attempt. The desire to set a good example for children and concern about being dependent on smoking are reasons smokers give for wanting to quit. Acute illness can also trigger cessation activity.

Smokers at younger ages, with higher levels of education and income, who smoke fewer cigarettes per day are more likely to try to quit. The forces influencing smoking cessation attempts may be different from those that lead to longer-term successful cessation. For example, older smokers are less likely to report making a cessation attempt in the last 12 months, but they are more likely to successfully quit for 3 or more months based on that cessation attempt. This observation suggests that efforts to promote cessation among older smokers can yield important cessation benefits even in the face of their lower rates of cessation attempts.

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Web Sites

HYPERLINK http://www.cdc.gov/tobacco/statehi/statehi.htm
http://www.cdc.gov/tobacco/statehi/statehi.htm
CDC Web site for State specific Tobacco Control Information
HYPERLINK http://www.econ.ag.gov/Briefing/tobacco/
http://www.econ.ag.gov/Briefing/tobacco/
Department of Agriculture Web Site for tobacco consumption data
HYPERLINK http://text.nlm.nih.gov/ftrs/tocview
http://text.nlm.nih.gov/ftrs/tocview
Agency for Health Care Policy Research web site for Clinical Practice Guidelines
HYPERLINK
http://www.mfmdesign.com/NCI_WEBSITE/NCI_MONOGRAPHS/LIST.HTM
http://www.mfmdesign.com/NCI_WEBSITE/NCI_MONOGRAPHS/LIST.HTM
NCI Web site for Tobacco Control Monographs

X. IDIOPATHIC, IMMUNOLOGIC, AND GRANULOMATOUS DISEASES

91. SARCOIDOSIS

Richard A. Bordow

Sarcoidosis is a multisystem granulomatous disease that most commonly affects young adults 20 to 40 years of age. It presents with bilateral hilar adenopathy, pulmonary infiltration, and ocular and skin lesions. The disease occurs worldwide, but the reported incidence reflects striking geographic and racial differences. In the United States, the condition occurs 10 times more frequently in the African-American population and more frequently in females. It is very common in Scandinavia and among Irish women in England but less common in Japan.

The cause of sarcoidosis has been the focus of much investigation, but still remains unknown. Early studies suggested a number causative agents, both environmental (e.g., metals—beryllium, zirconium, and aluminum, organic and inorganic dusts) and infectious (e.g., *Mycobacterium tuberculosis*, nontuberculous mycobacteria, fungi, spirochetes, and so on), but none survived the tests of reproducibility and universality. Whatever the *trigger*, recent data suggest that immunologic mechanisms involving cytokine-producing $CD4^+$ T-cell helper 1–lymphocytes and mononuclear phagocytes may be responsible for the lung damage and for the formation of noncaseating granulomas—the pathologic hallmark of sarcoidosis. Nonspecific monocytic alveolitis is seen early in the disease course. The initial trigger for this process is unclear but it may include immunologic, genetic, toxic, and infectious factors. Subsequently, a series of events lead to enhanced fibroblast replication. Despite the increased immunologic activity, cutaneous anergy is commonly present, probably reflecting the depletion of immunologic factors responsible for local reactions.

The clinical manifestations of sarcoidosis are protean, reflecting its multisystem involvement. Pathologically, the most commonly involved organ systems are the lungs (90%), peripheral lymphatics (50% to 75%), skin (10% to 30%), liver (60% to 80%), eye (17%), spleen (15%), bone (1% to 35%), salivary glands (5%), joints (10% to 15%), and heart (30%). Clinical manifestations occur at a much lower rate, because sarcoid lesions may be present in some organs without affecting their function. Cough and dyspnea are the most common respiratory complaints; chest pain, sputum production, and hemoptysis can also occur. Cor pulmonale occurs in 1% to 4% of cases, usually in the presence of severe fibrocystic sarcoidosis. Erythema nodosum is seen occasionally with the *typical* presentation of bilateral hilar adenopathy and connotes a good prognosis. Approximately 30% of patients are asymptomatic and only an abnormal chest radiograph identifies the disease. By international convention, the chest roentgenogram is staged as follows: *stage 0*, clear chest roentgenogram (5% to 16% of cases at presentation); *stage 1*, bilateral hilar adenopathy (25% to 40%); *stage 2*, bilateral hilar adenopathy with pulmonary infiltrate (24% to 49%); and *stage 3*, pulmonary infiltrates without hilar adenopathy (6% to 15%). Some investigators characterize a stage 4, in which pulmonary fibrosis or destruction occurs without adenopathy. It is unclear whether the *lower stages* represent milder forms of the disease or just early presentations of sarcoidosis that will eventually progress to more severe stages. Pleural disease occurs uncommonly and can be associated with lymphocytic exudative or transudative effusions. Computed tomography (CT) of the chest is more sensitive than a standard chest radiograph in defining the presence of thoracic lymph node enlargement, the pattern of parenchymal disease, and the presence of pleural involvement. CT generally is not recommended as part of the initial workup; however, it may be helpful in planning a biopsy procedure. High-resolution thin section CT may identify a pattern of parenchymal involvement relatively specific for sarcoidosis: nodular infiltrates adjacent to central bronchovascular structures.

The spectrum of pulmonary function impairment is broad. Pulmonary spirometric testing most commonly reveals a restrictive pattern, although a subset of patients may demonstrate a reversible obstructive pattern. A reduction in lung compliance

and diffusing capacity is part of the usual pattern of impairment. Hypoxemia may be present at rest or during exercise. The degree of functional impairment cannot be accurately predicted from the radiograph and vice versa. Serial pulmonary function evaluation is often useful, both in selecting patients for therapy and in following them while on medication.

The diagnosis of sarcoidosis is based on (1) the presence of a compatible clinical picture; (2) the exclusion of other granulomatous disease; and (3) histologic evidence of noncaseating granulomas on tissue biopsy. The histologic picture is not pathognomonic, and tuberculosis, fungal disease, beryllium disease, drug reactions, and local sarcoid reactions must be excluded. Bilateral hilar adenopathy in the presence of erythema nodosum or uveitis or in the patient who is asymptomatic strongly suggests sarcoidosis rather than an infectious or neoplastic process. Laboratory tests are generally not helpful in making a diagnosis. Angiotensin-I-converting enzyme (ACE) is a dipeptidyl carboxypeptidase that is found in normal lung in the luminal surface of capillary endothelial cells. Levels of ACE are increased in 60% to 80% of patients with sarcoidosis, but this finding is not specific because increased levels are also found in other disorders such as Gaucher's disease, leprosy, lymphangiomyomatosis, diabetes mellitus with severe retinopathy, alcoholic cirrhosis, and hyperthyroidism. This test should not be used for screening; rather, it should be interpreted in light of the other clinical conditions in which it can be elevated. Bronchoalveolar lavage (BAL) fluid demonstrates increased numbers of CD4 T-helper lymphocytes.

Gallium 67 (^{67}Ga) lung scanning is a noninvasive radioisotope technique that reflects, to a degree, the activity of the lung involvement in pulmonary sarcoidosis. The pattern of radioactive highlighting of bilateral hilar and right paratracheal lymph nodes has been termed the *lamda* sign; the highlighting of parotid, lacrimal, and salivary glands, the *panda* sign; the presence of both lamda and panda signs are somewhat specific for sarcoidosis. As with measurement of ACE, however, the presence of increased parenchymal radioactive update is nonspecific and is abnormal in other conditions such as interstitial pneumonia, silicosis, infections, and asbestosis. Most clinicians do not perform routine gallium scanning in view of the lack of specificity, radiation exposure, and cost. When tissue diagnosis is required, biopsy of an abnormal lymph node, parotid gland, nasal mucosal lesion, or other involved site almost always yields the diagnosis. Other methods of diagnosis are transbronchial lung biopsy (91% yield), mediastinoscopy (96%), open lung biopsy (100% yield), liver biopsy (70%), blind scalene-node biopsy (40% to 70%), blind bronchial mucosal biopsy (50%), and blind subconjunctival biopsy (50%). The selection of any of these procedures should be guided by the clinical presentation, with careful explanation of the risks and benefits to the patient.

Therapy for sarcoidosis is mandatory when evidence is seen of significant vital organ involvement or when the patient has marked systemic symptoms. The most urgent indications for treatment are symptomatic ocular, myocardial, and central nervous system disease. Other relative indications are persistent hypercalcemia, disfiguring cutaneous lesions, persistent or progressive symptomatic respiratory disease, thrombocytopenia, and severe constitutional symptoms. The most difficult treatment issue pertains to the asymptomatic individual with stable lung infiltrates persisting for a period of time (1–2 years) without reduction in pulmonary function. Some lung physicians tend to treat the patient with corticosteroids for a period of 2 to 3 months to determine the disease reversibility and diminish the prospect of permanent fibrosis, whereas others reserve treatment for those who demonstrate declining function.

Steroids remain the drugs of choice for pulmonary sarcoidosis. Most patients (~80%) require no therapy; however, treatment is indicated for significant functional impairment. If impairment is not severe, it would seem prudent to withhold steroid therapy and observe the patient carefully, as many patients improve spontaneously. Most therapeutic regimens use prednisone (30–60 mg/d), with tapered dosages over an interval of 6 months or more until a response is observed. In the presence of a positive tuberculin reaction or complete anergy, isoniazid should be given concomitantly with steroids. Exacerbations can occur when prednisone is decreased below 15 mg/d. Little experience has occurred with alternate-day regimens, but clinical trials seem warranted in view of the hazards of daily steroids. The effect of therapy on radiologic change is inconsistent. Therapy is best monitored by serially evaluating the clinical resolution of the original

therapeutic indication (e.g., pulmonary function deficits, uveitis, arthritis). Serial assessments of ACE, ^{67}Ga scanning, and BAL to monitor the course of sarcoidosis and the response to steroid therapy are of unproved benefit; most experienced clinicians do not rely on these tests. Inhaled corticosteroids have been used but their role is unclear. Immunosuppressive agents are occasionally used for pulmonary indications, but the results are disappointing in most cases. Methotrexate has been used as an alternate to steroids in treating pulmonary sarcoidosis with varying degrees of success. Azathioprine has also been used in corticosteroid-resistant sarcoidosis. Anecdotal experience suggests that it can be helpful in some patients; steroids are usually prescribed concomitantly. Chloroquine, intradermal steroids, methotrexate, and retinoids appear to be effective in managing skin disease. Topical steroids may be effective in treating uveitis. Organ transplantation has been used successfully for lung, heart, kidney, and liver disease in a small number of patients. Noncaseating granulomas have recurred in the transplanted organ in a few of these cases, according to reports.

The prognosis of sarcoidosis is generally favorable. About two thirds of patients with sarcoidosis who present with an abnormal chest x-ray film will completely clear or improve within 2 years. Of the remaining one third, the course is generally that of gradual decline over a period of a decade or more. About one half of this group with persistent activity will have fatal outcomes, usually from pulmonary insufficiency and cor pulmonale. The worst prognosis is experienced by patients with stage 3 disease. Death from sarcoidosis is a rare outcome among patients with stage 1 disease. Pulmonary complications include hemoptysis, mycetomas, and cor pulmonale.

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92. WEGENER'S GRANULOMATOSIS, CHURG–STRAUSS SYNDROME, AND RELATED DISORDERS

Kevin M. Murray

Wegener's granulomatosis (WG) is a systemic granulomatous vasculitis that can involve any organ system, but most frequently affects the upper respiratory tract, the lungs, and the kidneys. A class of autoantibodies named *antineutrophil cytoplasmic antibodies* (ANCA) is closely associated with WG and other forms of vasculitis, and may contribute to the pathogenesis of these disorders.

Most patients with WG have involvement of the upper or lower respiratory tracts. Because of this, it has been hypothesized that an inhaled infectious agent may, in some way, be responsible for the disease, causing disease in susceptible patients. Upper respiratory symptoms in WG include chronic sinusitis, rhinorrhea, bloody nasal drainage, sinus pain, otitis media, and nasal or oral ulcerations. Tracheal involvement can lead to airway obstruction and stridor. Biopsies of affected nasal mucosa may show characteristic granulomatous vasculitic changes, but pathologic findings in severely inflamed or infected tissue can be nonspecific.

Pulmonary symptoms can include cough, pleuritic chest pain, dyspnea, or hemoptysis. The disease is frequently misdiagnosed as pneumonia, which appears to be resistant to treatment. Rarely, WG can present as fulminating pulmonary hemorrhage leading to respiratory failure, or as an acute lung injury syndrome. Up to one third of patients with pulmonary findings may be asymptomatic.

Radiographic findings in pulmonary WG include consolidation, solitary or multiple nodules that frequently cavitate, pleural effusions, and localized interstitial infiltrates. Hilar adenopathy does not occur. One characteristic roentgenographic finding is the simultaneous waxing and waning of different infiltrates as inflammation occurs or resolves in different lung regions. Sinus x-ray films may show air–fluid levels.

Renal involvement is common in WG, seen in up to 80% of patients. Microscopic hematuria and red cell casts may be seen on urinalysis, and renal biopsies show varying degrees of inflammation, from a focal or segmental glomerulitis to a rapidly progressing necrotizing glomerulonephritis. Immunofluorescence shows this to be a *pauci-immune* glomerulonephritis, with absent or nearly absent immunoglobulin deposits. Glomerulonephritis can precede pulmonary WG by a period of months to years.

Other manifestations of WG include arthralgias or myalgias, mono- or polyarthritis, fever, weight loss, neurologic symptoms including mononeuritis multiplex, skin lesions, and pericarditis. Lesions of WG have been found in nearly all organs, testifying to the systemic nature of this vasculitis.

In the 1980s, a new class of autoantibodies to specific antigens in neutrophils was discovered. These antibodies, known as *antineutrophil cytoplasmic antibodies* (ANCA), were found to be present in many patients with several forms of systemic vasculitis, including WG, microscopic polyangiitis, the Churg–Strauss syndrome (CSS), and others.

Two patterns of indirect immunofluorescence were described: a diffuse cytoplasmic pattern (cANCA) and a perinuclear pattern (pANCA). The specific antigens involved have been identified. Myeloperoxidase is the target of pANCA and proteinase 3 (PR3) is the usual target of cANCA. Antibodies against a number of other neutrophilic antigens can cause cANCA or pANCA immunofluorescence, which can be detected by enzyme-linked immunosorbent assay (ELISA) methods.

The cANCA associated with WG is almost always an anti-PR3 antibody. Therefore, it is prudent to confirm a finding of cANCA by a specific ELISA assay for anti-PR3. The sensitivity of ANCA for *active* WG is approximately 90%, and the specificity is 99%. Inactive disease is much less likely to manifest ANCA, and up to one third of patients with limited WG do not show evidence of ANCA. The contribution of ANCA to the pathogenesis of WG is unclear—the ANCA may be an epiphenomenon related to neutrophil activation or it may enhance the activation and oxidative ability of neutrophils. It has also been suggested that an imbalance between PR3 and its primary inhibitor, α_{-1} antitrypsin, somehow predispose patients to WG.

Titers of ANCA rise and fall in relation to disease activity in two thirds of patients. However, this correlation is not sufficiently precise to allow adjustment of disease management based solely on ANCA levels. Specifically, a rising ANCA level should not be used as the sole reason for re-instituting therapy for a patient in clinical remission. Such patients should be followed closely for clinical signs of relapse.

The diagnosis of WG is made by tissue biopsy. Biopsy of lesions in the upper respiratory tract, which are frequently diagnostic, are relatively easy to obtain. Kidney biopsy may demonstrate a characteristic pattern of segmental necrotizing glomerulonephritis. Transbronchial lung biopsy is of limited usefulness, and most authorities recommend open or thoracoscopic lung biopsy as the invasive procedure of choice for the diagnosis of pulmonary disease.

For untreated patients with WG, the 2-year mortality rate is 90%. Combination therapy with cyclophosphamide and prednisone has been well established as the *gold standard* of therapy after some 30 years of experience. The *National Institutes of Health (NIH) protocol* uses an initial oral dose of cyclophosphamide (2 mg/kg/d) in combination with prednisone (1 mg/kg/d). Fulminant or life-threatening disease has been treated with higher doses of steroids, including *pulse* doses of intravenous methylprednisolone.

Several alternatives to cyclophosphamide and prednisone in the treatment of WG have been reported. Trimethoprim–sulfamethoxazole (TMP–SMX) has been beneficial for patients with limited WG confined to the upper respiratory tract. One report demonstrated that prophylaxis with TMP–SMX, one double-strength tablet twice daily was effective in preventing relapses over a 24-month period. Methotrexate has been used as an alternative to cyclophosphamide in the treatment of WG. Low-dose, intravenous therapy (0.3 mg/kg weekly) has been shown to be effective in reducing relapses of WG. Other agents that have been used successfully in the treatment of WG include cyclosporine and etoposide.

Among other vasculitides that can involve the lungs, the *Churg–Strauss syndrome*, allergic angiitis and granulomatosis, is the most common, amounting to approximately 10% of all vasculitides. This disorder is classically characterized by asthma,

eosinophilia, and systemic vasculitis. In 1990, the American College of Rheumatology established six criteria for the diagnosis of CSS: asthma, eosinophilia more than 10%, sinusitis, pulmonary infiltrates, mononeuritis multiplex, and demonstration of vasculitis on biopsy. The presence of four of these criteria had a sensitivity of 85% and a specificity of 99.7% for CSS.

A vasculitis of small- and medium-sized vessels is seen in CSS. Multiple organ systems may be affected, including the skin, nervous system, musculoskeletal system, gastrointestinal tract, kidney, eye, and heart. Involvement of the myocardium or the gastrointestinal tract has been shown to be associated with a poor prognosis. Radiographic findings in CSS most frequently consist of migratory interstitial or alveolar opacities, which generally do not cavitate. Infiltrates usually resolve quickly after initiation of therapy. Treatment for CSS consists of corticosteroids, which are usually effective. Cytotoxic agents may be useful in severe or resistant cases.

Recently, CSS has been reported to occur in certain asthmatic individuals following the institution of therapy with leukotriene inhibitors. Initially described following montelukast, a syndrome similar to CSS has been seen after use of most available drugs of this class. The pathogenesis of this association is believed to be related to an *unmasking* of latent CSS in patients who were mistakenly diagnosed as simple asthmatics but whose vasculitis was suppressed by corticosteroid medications. The addition of a leukotriene inhibitor then allowed steroid doses to be reduced, with the subsequent appearance of typical signs and symptoms of CSS.

Pulmonary involvement in other systemic vasculitides is unusual. Giant cell arteritis can present as a chronic cough, with normal radiographic studies, or rarely as pulmonary arterial thrombosis or infarction. Takayasu's arteritis can involve the pulmonary arteries, causing occlusion, stenosis, and dilatation. Behçet's syndrome can cause pulmonary arterial aneurysms, which can lead to hemorrhage, thrombosis, or infarction of lung tissue. Vasculitis in Behçet's syndrome can also lead to bronchial or tracheal stenosis. Polyarteritis nodosa, or the related disorder microscopic polyangiitis, also, rarely, can involve the lungs, causing diffuse pulmonary hemorrhage, vasculitis of pulmonary or bronchial arteries, diffuse alveolar damage, or interstitial fibrosis.

Lymphomatoid granulomatosis can mimic WG in the lungs, with x-ray film showing multiple nodules, which may cavitate, or diffuse reticulonodular infiltrates. The skin, upper respiratory tract, and nervous system may be involved. Histopathologic examination shows a lymphoid infiltrate that forms nodular lesions with necrosis and a lymphocytic angiitis; despite the name of the disorder, true granulomas are not seen. This disease is now felt to be a lymphoproliferative disorder with vasculitis. Atypical lymphocytes in these lesions have been found to be of B-cell origin, and mounting evidence indicates that infection by the Epstein–Barr virus may be associated with this disorder. Current treatment of lymphomatoid granulomatosis is with combination chemotherapy directed against B-cell lymphomas.

Bronchocentric granulomatosis is a disease that is confined to the lungs; it demonstrates granulomatous inflammation of the bronchi and peribronchial tissue. Up to one half of patients with bronchocentric granulomatosis have allergic bronchopulmonary aspergillosis (ABPA), with typical episodic wheezing, fleeting radiographic opacities, and serologic evidence of ABPA. Similar histopathologic findings have been seen in patients with fungal and mycobacterial infections, and these organisms must be carefully excluded, especially in the immunocompromised patient.

Necrotizing sarcoidal granulomatosis is felt to be a variant of sarcoidosis. The radiographic presentation may be that of solitary or multiple nodules, or a diffuse miliary pattern. Histopathologic examination of lesions demonstrates necrotizing granulomas, which may coalesce. Treatment with oral corticosteroids is usually effective.

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93. GOODPASTURE'S SYNDROME

Beat Walder

Goodpasture's syndrome refers to a clinical entity of pulmonary hemorrhage and glomerulonephritis. Historically, the eponym, *Goodpasture's syndrome*, has been applied inconsistently. Some clinicians restrict its use to the presence of alveolar hemorrhage and glomerulonephritis associated with circulating or tissue-bound antiglomerular basement membrane antibodies (AGBMA); others refer to it as any syndrome of glomerulonephritis and alveolar hemorrhage, regardless of cause or mechanism. This chapter focuses on disease associated with AGBMA. The targets of the antibodies are the basement membranes found in lungs and kidneys. It is likely that patients described in the 1950s and 1960s, before the development of the AGBMA assay (1970s), represented a mixture of causes and mechanisms.

A rare disorder, AGBMA disease has an estimated incidence of about 0.1 patients per 1 million population. It is more frequent in men than in women, with reported gender ratios ranging from 1.2:1 to 8:1. The disease has a bimodal peak in age of presentation; most patients present in their third or fourth decade, whereas a smaller number present in the fifth and sixth decades.

Approximately 60% of patients with AGBMA disease have pulmonary and renal manifestations of Goodpasture's syndrome. Pulmonary involvement can precede renal involvement by up to 12 months. Less commonly, nephritis precedes the onset of pulmonary hemorrhage. Isolated renal involvement is seen in approximately 40% of patients; isolated pulmonary involvement is unusual. The usual duration of symptoms preceding the diagnosis of AGBMA disease is weeks to months.

Clinically, patients with Goodpasture's syndrome complain of minimal to massive hemoptysis (72% to 82%), dyspnea (44% to 64%), and gross hematuria (up to 41%). Nonspecific symptoms (e.g., nausea, vomiting, diarrhea, and weight loss) are also common. Fever at presentation is uncommon, but a history of preceding flulike symptoms or upper respiratory tract infection may be elicited in up to 44% of patients. Patients with isolated glomerulonephritis present most commonly with nonspecific symptoms (55%) and gross hematuria (44%). The most common clinical signs in Goodpasture's syndrome include pallor (76%) and crackles (47%). Pallor in patients with isolated glomerulonephritis is seen in approximately 53% of patients.

Laboratory examination in AGBMA disease discloses anemia in 77% of patients, with a mean hemoglobin level at the time of presentation of 8.6 g/dl. Abnormal urinalysis (hematuria, proteinuria, or nephritic sediment) is common (71% to 100%).

The chest radiographic findings in patients with Goodpasture's syndrome are often nonspecific and are of limited value in the differential diagnosis. The chest radiograph most frequently shows bilateral, symmetric air space filling in the middle and lower lung zones. Less common are asymmetric, focal, or interstitial abnormalities. Resolution of infiltrates generally occurs over days. Pleural effusions in the absence of infection or volume overload are rare. The chest radiograph can be normal, even in the presence of hemoptysis. Long-term radiographic abnormalities have not been reported.

Pulmonary function testing often reveals mild restriction and decreased diffusing capacity for carbon monoxide/alveolar ventilation (DLCO/VA). However, elevated DLCO/VA values will occur during pulmonary hemorrhage, even in the absence of either hemoptysis or abnormal chest radiograph findings. Serial measurements of DLCO/VA have been advocated as a noninvasive diagnostic tool to detect recurrent pulmonary hemorrhage. At long-term follow-up, patients with AGBMA disease with pulmonary hemorrhage have lower DLCO/VA values than patients without hemorrhage and controls.

The pulmonary histopathologic findings in AGBMA disease are nonspecific. During acute alveolar hemorrhage, both red blood cells and hemosiderin-laden macrophages are commonly present, the latter finding indicating the presence of chronic alveolar hemorrhage. Neutrophilic capillaritis can be seen. Immunofluorescent studies may demonstrate characteristic linear deposition along the alveolocapillary basement membrane of IgG and (often) complement.

The finding of bloody pulmonary secretions and hemosiderin-laden macrophages obtained by bronchoscopy with bronchoalveolar lavage can provide indirect evidence of alveolar hemorrhage. Assessment of the major airways and collection of specimens for microbiologic studies can also be accomplished at the time of bronchoscopy. Transbronchoscopic lung biopsy for immunofluorescent studies in patients with AGBMA disease and hemoptysis has had variable success, the yield ranging from 30% to 100%.

The renal pathologic findings typically demonstrate focal or diffuse proliferative glomerulonephritis with crescent formation, although other forms of glomerulonephritis have been described. Immunofluorescent studies of the glomerular basement membrane are of key diagnostic importance. Although IgG deposits along the basement membranes are characteristic, they are considered diagnostic only in the context of serologic confirmation of AGBMA. In their absence, elution studies of IgG deposits from kidneys may demonstrate their specificity against the glomerular basement membrane.

The likely autoantigen in AGBMA disease has been localized to the noncollagenous (NCl) domain of the 3 chain of type (IV) collagen. Type (IV) collagen is one of the main structural components in basement membranes. Each type (IV) collagen molecule consists of three α chains that form a triple helix except in the C-terminal end where they form separate globular structures, the NCl domains.

Antibodies directed against the α3(IV)NCl domain were found in all sera tested in several studies, whereas specificities against other chains were also detected. Isolated α3(IV) chains probably contain no additional epitopes beyond the NCl domain. Mounting evidence points to the N-terminal region of α3(IV)NCl as carrier of the important epitope(s). Whether additional epitopes are found after reconstitution of the entire type (IV) collagen molecule remains to be seen.

The pathogenetic potential of antiglomerular basement membrane antibodies has been shown in a classic transfer experiment in which antibodies eluted from patients induced glomerulonephritis in recipient monkeys. More recent investigations have focused on the interaction of neutrophils, cytokines, adhesion molecules, and complement in the pathogenesis of the disease. The role of T-cell immunity in this disorder is also being investigated.

More than 90% of patients with Goodpasture's syndrome have circulating AGBMA. Different assays using a variety of glomerular basement membrane antigenic preparations are available: indirect immunofluorescent study, radioimmunoassay, and, more recently, enzyme-linked immunosorbent assay and immunoblotting. Both radioimmunoassay and enzyme-linked immunosorbent assay are very sensitive and specific and more sensitive than indirect immunofluorescent study. Immunoblotting serves as a confirmatory test. Attempts at correlating AGBMA titers with specific clinical or laboratory findings have shown contradictory results. AGBMA titers decrease faster with therapy than without and are used to monitor response to therapy.

The cause of AGBMA disease remains unknown. It is likely that a combination of genetic predisposition and environmental stimuli are responsible. In terms of the genetic background, a strong association with certain HLA antigen class II genes has been found. HLA-DRw15, a subspecificity of DR2, was present in 76% of patients with AGBMA as compared with 31% of controls; HLA-DR4 may also contribute to the genetic risk. The presence of HLA-DRw2 and HLA-B7 has been linked to more severe glomerulonephritits and worse prognosis. The list of associated environmental factors is extensive and includes cocaine use, extracorporeal shock wave lithotripsy, exposure to hydrocarbons and hard metal dust, cigarette smoking, and influenza A2 virus infections.

The diagnosis of AGBMA disease is established by a compatible clinical presentation (alveolar hemorrhage, glomerulonephritis, or both) and demonstration of either circulating or tissue-bound AGBMA. Kidney biopsies are frequently performed and have a very high diagnostic yield if renal abnormalities are present. Even in the presence of circulating AGBMA, kidney biopsies can add to the evaluative process: (1) AGBMA can be demonstrated with direct immunofluorescent studies; (2) accompanying or alternative lesions can be assessed; and (3) additional prognostic information (e.g., the percentage of crescent glomeruli) may be obtained. Lung biopsy, which usually does not add to the information obtained from documenting AGBMA disease serologically or by renal biopsy, is rarely indicated.

The differential diagnosis for patients presenting with diffuse alveolar hemorrhage or Goodpasture's syndrome is broad and a combination of clinical and laboratory data is

often needed to establish a definitive diagnosis. The most common competing diagnoses are Wegener's granulomatosis (WG), microscopic polyarteritis (systemic necrotizing vasculitis), systemic lupus erythematosus (SLE), and idiopathic glomerulonephritis with alveolar hemorrhage. Determination of serum autoantibodies such as antineutrophil cytoplasmic antibodies (ANCA), AGBMA, and antinuclear antibodies (ANA) as well as complement levels may be invaluable in the diagnostic process. Rapid screening assays for AGBMA and ANCA have been developed. Less common underlying conditions include rheumatoid arthritis, Behçet's disease, Henoch-Schönlein purpura, antiphospholipid antibody syndrome, mixed cryoglobulinemia, pulmonary cholesterol emboli, pulmonary hemorrhage after bone marrow transplantation, idiopathic pulmonary hemosiderosis, certain localized and metastatic tumors, drug reactions (e.g., penicillamine, cocaine), mitral stenosis, and pulmonary veno-occlusive disease.

The optimal therapeutic approach for the spectrum of AGBMA disease has not been established. A variety of therapeutic options for AGBMA disease have been described. The most common initial regimen is a combination of prednisone (1–2 mg/kg/d, at times preceded by pulse methylprednisolone), cyclophosphamide (1–3 mg/kg/d), and plasmapheresis (initially 10–14 exchanges, then individualized). Azathioprine (1–2 mg/kg/d) is also used. Immunosuppressive regimens are usually tapered over weeks to months, based on the clinical course. The therapeutic regimens described in the literature vary in many aspects, thus making comparisons among them difficult.

Mortality and morbidity rates remain significant: In larger studies, approximately 14% (range 6% to 32%) of patients with AGBMA disease die from complications of the disease. Of those who survive, approximately 53% progress to or remain in end-stage renal failure, requiring maintenance dialysis or renal transplantation.

Some important prognostic principles have emerged regarding the evaluation of the outcome of patients with AGBMA: (1) AGBMA disease presents with a wide spectrum of severity, from asymptomatic laboratory abnormalities to fulminant disease with high morbidity and mortality rates despite therapy; (2) severe disease at presentation (serum creatinine >6.8 mg/dl) has a very poor prognosis in regard to renal function with a 4% (range 0 to 18%) recovery of independent renal function despite therapy; (3) patients with mild forms of the disease (serum creatinine <6.8 mg/dl and <50% of glomeruli affected by crescents) generally do well, with approximately 87% of patients maintaining or regaining independent renal function, some even without specific therapy.

Current treatment regimens with high-dose corticosteroids, plasmapheresis, or both control alveolar hemorrhage in most patients; however, approximately 27% (range 0 to 100%) of eventual deaths are attributed to alveolar hemorrhage.

Chronic courses of Goodpasture's syndrome, with relapses (worsening clinical manifestations while AGBMA still present) and recurrences (manifestations after an interval of clinical quiescence and normalized AGBMA titer) have been described. Relapses have been attributed to resumption of smoking and bacterial infections. The rare recurrences are usually accompanied by elevated AGBMA titers, especially when testing is done using sensitive assays. Treatment is the same as that described for the initial presentation.

Up to 30% of patients with AGBMA disease also have serum ANCA. One study suggested that patients positive for both antibodies have a better prognosis in terms of their renal disease.

Renal transplantation is a promising therapeutic option for patients with end-stage renal disease secondary to AGBMA disease. Renal transplants are usually delayed until AGBMA titers have normalized for 9 to 12 months. A 5-year graft survival of 44% has been reported. Recurrent disease in transplanted kidneys was responsible for 14% of graft failures.

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94. IDIOPATHIC PULMONARY HEMOSIDEROSIS

William L. Ring

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease of unclear cause and pathogenesis characterized by the abnormal collection of hemosiderin in the lungs. It is primarily a disease of the first decade of life, but may be diagnosed in adults. Equal gender

distribution is seen and at least some cases have a genetic predisposition. IPH is characterized by iron deficiency anemia and recurrent or chronic pulmonary symptoms (e.g., cough, hemoptysis, and dyspnea). It is associated with diffuse parenchymal infiltrates on chest roentgenogram. The dominant histopathologic features are intra-alveolar hemorrhage and hemosiderin-laden macrophages. Diagnosis of this disease is essentially an exclusionary process, which generally requires ruling out the presence of coagulopathy, hemodynamic abnormalities (congestive heart failure, mitral stenosis), and infection, as well as systemic disorders such as vasculitis, immune-complex disease, or antibasement membrane antibody disease. The outcome of IPH is highly variable, ranging from decade-long periods of remission to sudden death from massive hemoptysis. The median survival is usually reported to be approximately 3 years after diagnosis, although at least one recent study reports much better prognosis. Treatment is largely supportive, although immunosuppressive drugs seem to be associated with improvement in some patients.

Idiopathic pulmonary hemosiderosis has a highly variable presentation. Patients may present with hemoptysis, which tends to be episodic. Although the hemoptysis can be massive, it is often mild and can be absent despite significant intrapulmonary bleeding. Intrapulmonary bleeding may initially be clinically silent. An iron deficiency anemia can overshadow clinical or roentgenographic pulmonary abnormalities. Chronic cough, fatigue, dyspnea, and pallor are frequent. Occasionally, pulmonary hypertension develops. The chest roentgenogram at the time of an acute hemorrhage may show diffuse mottled densities, which are particularly prominent in the perihilar regions and lower lung fields. In 2 to 3 days, the consolidation is replaced by a reticular pattern that resolves over 10 to 14 days. With repeated bleeding episodes, progressive interstitial changes can develop in a pattern of interstitial fibrosis, which can become massive. Hilar lymph nodes may be enlarged, particularly during acute episodes. Computed tomography (CT) findings confirm the chest roentgenogram findings. Magnetic resonance imaging may specifically diagnose a new hemorrhage because of the paramagnetic effect of ferric iron. Pulmonary function studies show a restrictive pattern, with an elevation of the carbon monoxide diffusing capacity during episodes of bleeding. Often a transient obstructive component is seen. The histologic findings are nonspecific, but an open lung biopsy is often required to exclude other diagnoses. Findings include alveolar hemorrhage, hemosiderin-laden macrophages, hyperplasia of the alveolar epithelium, and variable degrees of fibrosis. Vasculitis, necrosis, and granuloma formation are absent. Immunofluorescent stains are negative for immune deposits at the basement membranes, and inflammatory changes are minimal.

Although IPH can be associated with a number of diseases and environmental factors, it remains a disease of unclear cause. A number of reports have noted an association between celiac disease and IPH, and in some cases treatment of the celiac disease seemed to improve the course of the IPH. However, any pathogenetic link between the celiac disease and IPH remains controversial. Some reports have suggested that the IPH may be associated with low socioeconomic status, toxic exposure (insecticides, hydrocarbons), seasonal clustering (spring and fall), viral agents, or diet (cow's milk allergy). Reports have been made of exacerbation of IPH with pregnancy. Despite these findings, no consistent pattern remains to warrant conclusions regarding the cause of IPH.

Treatment of IPH is controversial. The results of therapy are difficult to interpret because of the natural variation in the clinical course of the disease and the small number of patients reported. No controlled therapeutic trials have been conducted. Corticosteroids remain the primary line of treatment, supported by clinical improvement in a number of case reports. However, the efficacy of high-dose corticosteroids during acute bleeding episodes remains unclear, and chronic steroid therapy may not alter the disease course. Case reports suggest that long-term treatment with moderate doses of inhaled steroids after stabilization with systemic steroids helps to control IPH. Claims have also been made of responsiveness of the disease to immunosuppressants, particularly azathioprine and chloroquine. However, separation of drug effects from spontaneous remission is difficult to ascertain.

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95. INTERSTITIAL PNEUMONITIS/FIBROSIS AND BRONCHIOLITIS OBLITERANS WITH ORGANIZING PNEUMONIA

Carla R. Lamb and Cecilia M. Smith

Interstitial pneumonia (IP) is a common pathologic response of the lungs to a wide variety of insults of known and unknown cause; it is often referred to as *interstitial pneumonitis* or *interstitial lung disease*. A multitude of drugs are capable of inciting IP, including antineoplastic agents (e.g., bleomycin and methotrexate), antimicrobials (e.g., nitrofurantoin and penicillin), and such diverse compounds as amiodarone and hydrocholorothiazide. IP also is a common response to both inhaled antigens (farmer's lung, pigeon-breeder's lung) and dusts (asbestos, silica). Viral agents, *Mycoplasma pneumoniae* and other infectious agents can cause IP. IP also develops among patients with many of the connective tissue diseases (e.g., lupus, scleroderma, rheumatoid arthritis). Clinically, the interstitial lung diseases (ILD) present with cough, dyspnea, hypoxemia, restrictive pulmonary function, and progressive interstitial changes.

In many cases of IP, the inciting agent is unknown and the disorder is classified as idiopathic IP (IIP). Until the 1960s, *idiopathic pulmonary fibrosis* (IPF) remained largely a clinical diagnosis; only 30% to 40% of patients actually had a histopathologic diagnosis established by open lung biopsy. As a result, this somewhat heterogeneous group was *lumped* together under the term. When considered as a single entity, IPF has been felt to be a terminal disease with a very poor prognosis because of the lack of significant response to immunosuppressive therapies—only 30% respond to such therapy. However, a retrospective review of clinical and histopathologic data allows IIP to be classified into distinct subsets that differ in clinical course, prognosis, and response to treatment: (1) usual IP (UIP), the category most authors use synonymously with IPF; (2) respiratory bronchiolitis-associated interstitial lung disease, also termed desquamative IP; (3) nonspecific IP (NSIP); and (4) the Hamman–Rich syndrome, also termed acute IP or diffuse alveolar damage. These categories represent histopathologic subsets with variable clinical courses. Other histologic subtypes that were linked to causative agents (e.g., lymphoid IP, associated with lymphoproliferative disease in the immunocompromised host) and giant cell IP (pneumoconiosis with hard metals such as cobalt) cannot be accurately termed IIP.

Approximately 30% of all interstitial lung diseases are caused by IPF. UIP is the most typical histology found in IPF; however, the same histology may be found in connective tissue disease. IPF has a 2:1 male predominance and a reported prevalence of 29 per 100,000 population. Most patients are more than 50 years of age and present with slowly progressive cough and dyspnea. One fourth of patients exhibit digital clubbing. Heterogeneous histopathologic features are seen within the same lung, containing zones of inflammation, interstitial fibrosis, collagen deposition, thickened alveolar septa, focal nests of proliferating fibroblasts, honeycombing with distorted alveolar architecture, and areas of normal lung parenchyma. The clinical course is insidious and, although survival and prognosis vary, the mean survival after diagnosis is 2.8 years. Few patients with IPF respond to immunosuppressive therapy. Approximately 30% of patients will clinically improve on combined therapy with prednisone and another immunosuppressive agent.

Respiratory bronchiolitis-associated lung disease was initially termed desquamative IP, because of the mistaken impression that the alveoli contained desquamating epithelial cells (which were later found to be macrophages). The disorder is strongly associ-

ated with current tobacco smoking and has a male predominance. Histopathologic features are homogenous and include peribronchiolar involvement, numerous intra-alveolar pigmented macrophages, and multinucleated giant cells. Honeycombing is rare, as are foci of fibroblasts. The clinical course is insidious, but has a good prognosis and high rate of spontaneous resolution if the patient stops smoking. It may also respond to steroid therapy.

An acute variant of ILD is described as acute IP, diffuse alveolar damage, and the Hamman–Rich syndrome. Considerable overlap is seen in the description of these entities, both clinically and histopathologically. The histopathology demonstrates uniform, diffuse, active, massive, interstitial fibrosis with occasional hyaline membrane formation. Clinically, patients have acute, rapidly progressive respiratory failure with low incidences of recovery. The syndrome is often preceded by an acute viral illness. The ongoing lung damage and respiratory failure respond poorly to immunosuppressive therapy.

Nonspecific IP has a slight female predominance (1.4:1). Clinical features that distinguish it from IPF are (1) its subacute progression; (2) its generally good prognosis; and (3) its good response to immunosuppressive therapy. Histopathologically, a highly cellular lymphoid predominant infiltrate is seen; fibrosis, if present, is mild. Bronchoalveolar lavage demonstrates a low CD4:CD8 ratio.

Some experts recommend thoracoscopic lung biopsy for all patients with ILD unless underlying comorbidities place the patient at high risk for complications. Previously, open lung biopsy was performed to rule out the presence of lung diseases other than the idiopathic interstitial pneumonitis (e.g., sarcoidosis, eosinophilic granuloma, hypersensitivity pneumonitis, connective tissue diseases, and lymphangitic carcinomatosis). However, lung biopsy may also help in identifying those subtypes of IIP who have better prognoses and treatment responses. For example, historically, some patients clinically diagnosed with IPF did not demonstrate UIP histopathologically; therefore, lung biopsy changed the clinical diagnosis and prognosis. High resolution computerized tomography (HRCT), using 1- to 2-mm collimation may distinguish between patients with IPF who may or may not respond to therapy. Responders have the appearance of *ground glass* alveolar filling processes; nonresponders demonstrate fibrosis, honeycombing, and other findings typically associated with UIP. CT scanning does not replace the need to establish the histopathologic entity by lung biopsy.

The diagnostic approach to the patient presenting with dyspnea, cough, and interstitial radiographic changes should begin with a thorough history, with special attention paid to (1) the clinical progression of symptoms such as cough, dyspnea, and exercise tolerance; (2) an environmental and occupational history, including exposure to drugs; (3) tobacco use; (4) connective tissue diseases; and (5), exposures or familial predisposition such as family history for similar symptoms. Common physical findings include the presence of end-inspiratory *velcro* crackles and, at times, clubbing. The physical examination may provide important causative clues, such as signs of connective tissue disease. Some findings (e.g., evidence of pulmonary hypertension and cor pulmonale) yield important prognostic information.

Chest roentgenograms typically disclose midbasilar and bilateral patchy airspace opacities or peripheral interstitial changes. In up to 10% of patients, findings on planar films will be normal. HRCT often reveals bilateral and diffuse ground glass opacities; in some cases, subpleural fibrosis, cysts, and traction bronchiectasis are also seen. As with planar films, a normal CT study does not rule out disease. Pulmonary function tests disclose reduction in static lung volumes (i.e., restrictive lung disease) and reduced carbon monoxide diffusing capacity (DLCO). If pulmonary fibrosis coexists with significant obstructive disease (i.e., emphysema), lung volumes can appear normal. Arterial blood gases, measured during rest or exercise demonstrate hypoxemia with a widened (A-a) gradient. Cardiopulmonary exercise testing may be more sensitive than HRCT in detecting mild abnormalities. Finally, serologic examination for hypersensitivity pneumonitis and connective tissue disease may be helpful in certain patients.

Histopathologic samples obtained by open lung biopsy or thoracoscopic lung biopsy may distinguish IP subsets and predict the patient's response to immunosuppressive therapy. Unfortunately, transbronchial biopsy does not provide sufficient tissue to allow an accurate analysis.

Clinical studies suggest that the results of the diagnostic work-up can be used to predict the likelihood of a patient's response to therapy. A poor response is associated with

(1) advanced age, (2) tobacco use, (3) DLCO less than 30% of predicted, (4) eosinophilia in bronchoalveolar fluid, and (5) fibrosis on lung biopsy.

The strategy of treating patients with IPF is to initiate treatment at the time of diagnosis. Treatment consists of prednisone (0.5–1 mg/kg/d) combined with an immunosuppressive agent such as cyclophosphamide (2 mg/kg/d) or azathioprine (2 mg/kg/d) based on ideal body weight. Commitment to a treatment course of at least 1 year should be planned, because a measurable response may not be seen until after 6 to 9 months of therapy. Serially performed objective tests (e.g., rest and exercise arterial blood gases, pulmonary function tests, and HRCT scans) can greatly enhance the clinical assessment of therapy response. These can be followed at 3-month intervals, unless symptoms warrant that they be performed more frequently. Research is ongoing to seek new therapies for IPF.

Of particular interest are therapies directed at those factors involved in fibroblast propagation, collagen synthesis, and the release of proliferative cytokines. Pirfenidone, an inhibitor of transforming growth factor-β, inhibits collagen synthesis. In a preliminary study, pirfenidone appeared to stabilize lung function in a small group of patients with IPF. Interferon γ-1b combined with *low dose* prednisolone recently has been compared with conventional prednisolone for IPF treatment. The results demonstrated a decrease in resting hypoxemia and improvement in total lung capacity for the interferon group.

The drug regimen of choice for non-UIP is also evolving and is dependent on the histopathology identified. A reasonable strategy is to initiate therapy with oral corticosteroids (e.g., prednisone) in a dose of 0.5 to 1.0 mg/kg/d (not to exceed 100 mg/d), for 4 to 6 weeks. Response is assessed at the end of this period and the dose is adjusted accordingly. If no response is noted, the steroid therapy is tapered off. If a response occurs, the same or a slightly modified dose is maintained and re-evaluation is carried out in 4 weeks. Thereafter, dosing is determined by evaluating patient response and steroid side effects. The usual sequence is to taper slowly to an alternate day regimen of 15 to 20 mg for 3 to 6 months. An attempt is then made to taper the steroids off. Often discontinuation is not possible and steroids are maintained long term (months to years), with periodic slow withdrawal to determine whether the patient is in remission.

Because of the adverse effects associated with high-dose steroids, immunosuppressive agents can be added to the regimen to lower or eliminate the necessity for steroids. After the initiation of therapy with high-dose corticosteroids, cyclophosphamide or azathioprine with colchicine can be added as steroid-sparing agents. Small clinical series have suggested that combined regimens with cyclophosphamide/prednisone or azathioprine/prednisone are more beneficial than prednisone alone. Larger studies are needed to further substantiate the potential benefits of these therapies.

Other therapeutic approaches include the use of bronchodilators in those patients who may have combined obstructive and restrictive disease. Infection prophylaxis with the influenza vaccine, pneumococcal vaccine, and *Pneumocystis carinii* prophylaxis in those patients on immunosuppressive regimens are beneficial. Lung transplantation should be anticipated early in the disease course for patients who are deemed candidates, as the waiting list for transplantation often exceeds the survival of the patient with UIP or IPF.

Although, strictly speaking, *bronchiolitis obliterans organizing pneumonia* (BOOP) is a histopathologic finding common to a number of diseases, the term is also used to describe a distinct clinical entity with characteristic radiographic findings. It should be considered in the patient presenting with a flulike illness, with patchy infiltrates on chest radiograph not responsive to antibiotics. No gender predominance and no association with tobacco use are seen. BOOP can be found in a number of different clinical settings such as postinfectious syndromes (e.g., cytomegalovirus, adenovirus, influenza, chlamydia, malaria); reactions to drugs (e.g., gold, sulfasalazine, methotrexate, bleomycin, amiodarone, cephalosporins, cocaine, phenytoin); collagen vascular diseases (rheumatoid disease, polymyositis); bone marrow, lung, and renal transplantation; and radiation therapy. Idiopathic forms occur in childhood and adulthood.

Radiographically, BOOP is characterized by migratory bilateral patchy alveolar infiltrates. HRCT demonstrates bilateral consolidation, predominantly in subpleural or peribronchial areas. Lung biopsy reveals an alveolar filling process with polypoid granulation tissue plugs that fill bronchial lumens. Also seen is distal bronchiolar inflammation.

The prognosis and response to immunosuppressive therapy is generally good. Reported recovery rates range from 65% to 85%. Treatment can begin with up to 1 mg/kg or 60 mg daily of prednisone for 1 to 3 months; the dose is then tapered according to clinical parameters.

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96. PULMONARY MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Frank D. Bender

Rheumatoid arthritis (RA) is a systemic inflammatory disorder whose pulmonary effects can be grouped into eight categories: (1) pleural disease; (2) interstitial pneumonitis; (3) drug-related pulmonary disease; (4) pulmonary nodules; (5) airways disease; (6) pulmonary vascular disease; (7) apical fibrocavitary disease; and (8) miscellaneous effects. Although frequently present as distinct entities, more than one manifestation can occur simultaneously or in sequence in an individual with rheumatoid disease.

Pleural disease is the most frequent pulmonary manifestation; it occurs as pleurisy in 20% of cases or as pleural effusion in 3% to 5%. In addition, asymptomatic pleural involvement is probably common, because autopsy series show pleural fibrosis or pleural effusion in approximately 50% of patients with RA. Despite that RA is more common in women, pleural disease has a striking predominance for middle-aged men. It can occur at any time during the course of the RA; in 20% of cases, however, it immediately precedes or occurs at the onset of arthritis. The presence of pleural disease appears to bear no definite relationship to the activity of the arthritis or to the titer of rheumatoid factor but correlates to some extent with the presence of subcutaneous nodules. Pathologically, the pleura shows chronic (mononuclear cell) inflammation; pleural or subpleural rheumatoid nodules may occasionally be seen.

Symptoms, which are usually minimal, are absent at least one third of the time. When present, symptoms can include pleuritic pain or cough. Rarely, a large effusion will cause dyspnea, especially in individuals with underlying parenchymal lung disease. Fever is infrequent. The chest roentgenogram reveals pleural thickening or effusion, which is unilateral in 80% of cases with a right-sided predominance.

A diagnostic thoracentesis is indicated to rule out malignancy or infection. The pleural fluid is characteristically a yellow-green color, although long-standing effusions may have an opalescent or milky quality from cholesterol crystals. Rheumatoid effusions are exudative and have elevated protein levels and lactate dehydrogenase levels frequently above 1000 U/L. The pH and glucose levels are low. The glucose is less than 50 mg/dl in 80% of cases and is less than 25 mg/dl in 66% of patients. The pleural fluid glucose fails to rise during intravenous infusions of glucose—a characteristic that distinguishes rheumatoid effusions from low glucose effusions caused by other diseases. The differential cell count is usually lymphocytic, but granulocytes can

predominate if the thoracentesis is done early on in the inflammatory process. Rheumatoid factor is present in higher concentrations than in the serum, but this is a nonspecific finding that occurs in effusions from other causes as well. Complement levels in pleural fluid can be sharply reduced in comparison with blood levels, a finding that distinguishes rheumatoid effusions and effusions secondary to systemic lupus erythematosus from those of other causes. A characteristic pleural fluid cytologic triad of elongated macrophages, giant multinucleated macrophages, and granular cell debris is felt to be diagnostic and should be sought. Mesothelial cells are nearly always absent.

The pleural effusions in RA tend to resolve spontaneously over the course of several months and frequently leave residual pleural thickening. Rarely, such thickening is sufficient to cause significant lung restriction and lead to consideration of pleural stripping. If the pleural disease causes significant dyspnea or other symptoms, therapeutic options include (1) nonsteroidal anti-inflammatory drugs (2) drainage by thoracentesis; (3) a trial of oral corticosteroids if the effusion recurs; and (4) pleurodesis. Approximately 20% of RA-associated pleural effusions will be persistent. Most of these, however, will resolve within 1 to 5 years. Empyema has been reported to complicate rheumatoid pleural effusion, possibly because of impaired local defense mechanisms in conjunction with necrosis of a subpleural necrobiotic nodule. Systemic steroids, if used, could contribute to or mask the presence of an empyema, and those undergoing this treatment should be monitored carefully.

Interstitial pneumonitis, historically and clinically indistinguishable from the idiopathic variety, occurs with greater than expected frequency in patients with RA. Conversely, 15% to 20% of patients with idiopathic interstitial pneumonitis either have a positive rheumatoid factor or develop symmetric polyarthritis consistent with RA during their clinical course. As with pleural disease, men are over-represented. Interstitial pneumonitis occasionally precedes the onset of arthritis. Patients are generally seropositive, but the activity of the arthritis bears no relationship to the occurrence or severity of the interstitial pneumonitis.

The exact incidence of interstitial pneumonitis in RA is unclear. Characteristic roentgenographic findings of interstitial pneumonitis, a diffuse reticulonodular infiltrate with basilar predominance, occurred in 1.6% in a series of 516 patients with RA. Other series show characteristic plain chest film abnormalities in up to 6% of patients. High-resolution computed tomography (HRCT) is more sensitive than a plain chest roentgenogram in detecting interstitial disease. Various series report interstitial abnormalities in 10% to 40% of patients. Pulmonary function test abnormalities occur frequently. One report describes abnormal pulmonary function in 41% of an unselected series of patients with RA, the majority of whom had no pulmonary symptoms. The carbon monoxide diffusing capacity (DLCO) is believed to be more sensitive than spirometry in detecting interstitial disease.

With a combination of imaging techniques, physiologic testing, and bronchoalveolar lavage, abnormalities suggesting interstitial lung disease can be seen in up to 58% of patients with recent onset RA. In 14%, the changes are clinically significant. Cigarette smoking is an important risk factor in the development of interstitial disease. Serologic tests for circulating levels of KL-6 (a MUC1 mucin) have been proposed as sensitive markers for active rheumatoid interstitial pneumonitis.

Nonproductive cough, exertional dyspnea, and easy fatigability are the most frequent symptoms. Clinical stability may be present for years or, rarely, a rapid progression toward respiratory failure is seen. Examination reveals characteristic fine *velcro* bibasilar crepitation. Subcutaneous nodules occur in most cases, and finger clubbing is quite common. Symptomatic individuals demonstrate hypoxemia (worsened by exercise), diminished DLCO, and reduced static lung volumes. The course of rheumatoid interstitial pneumonitis is variable.

The decision to treat rheumatoid-associated interstitial disease is based on the initial severity of symptoms and of physiologic impairment, as well as on the rate of deterioration over time. Initial treatment is usually with corticosteroids. Immunosuppressive agents (e.g., cyclophosphamide or methotrexate) can be tried in those who are unresponsive to corticosteroids or who are at risk for severe side effects from them. A poor prognosis for patients with RA hospitalized for evaluation or treatment of interstitial pneumonitis was recently reported, with a median survival of 3.5 years and a 5-year survival of 39%.

The possibility of drug-induced interstitial pneumonitis and of other pulmonary reactions to treatment must be kept in mind when evaluating patients with RA. Methotrexate causes pulmonary reactions in 1% to 5% of patients. Interstitial pneumonitis is most common. Other reactions include pleuritis, hilar adenopathy, and nodules. An eosinophilia may be seen up to 50%. Cough not associated with interstitial disease can occur, which is felt to be an irritant effect of methotrexate. Risk factors for the development of methotrexate-associated pulmonary toxicity include advanced age, diabetes, a low serum albumen, pre-existing interstitial abnormalities, and previous adverse reactions to disease-modifying antirheumatic drugs.

Gold can produce interstitial pneumonitis. Factors that can help in distinguishing gold-induced interstitial pneumonitis from rheumatoid-associated interstitial disease are a female predominance, the presence of a skin rash or fever, low titers of rheumatoid factor, a lymphocytosis in bronchoalveolar lavage fluid, and gold-specific chest CT findings. With both methotrexate and gold, treatment of pulmonary toxicity involves withdrawal of the drug and administration of corticosteroids.

Ibuprofen has been associated with hypersensitivity pneumonitis, pleural effusions, and exacerbation of asthma. Corticosteroids are associated with opportunistic pulmonary infections that can resemble an interstitial pneumonitis.

In general, the evaluation and management of possible drug-related pulmonary toxicity requires (1) excluding progression of rheumatoid interstitial disease and infection; (2) withdrawing the potentially offending drug (and not rechallenging); and (3) treating with corticosteroids, as appropriate.

A lung biopsy should be considered in cases (1) of rapidly progressive interstitial disease; (2) where concern exists regarding drug-induced disease or opportunistic lung infection; or (3) of unexplained fever.

Necrobiotic nodules in the lung parenchyma, either single (34% of cases) or multiple (66%), can occur at any time during the course of RA. They sometimes occur coincident with an exacerbation of joint symptoms. Necrobiotic nodules are more common in men and correlate with the presence of subcutaneous nodules. Histologically identical to subcutaneous rheumatoid nodules, they are characterized by palisading epithelial cells surrounding a central core of fibrinoid necrosis. These lesions tend to be asymptomatic unless very large, when they can cause compressive symptoms. They infrequently undergo cavitation, at which time minimal hemoptysis may be present. Few become infected. Nodules can rupture into the pleural space, resulting in bronchopleural fistulas, pleural effusions, pneumothoraces, or pyopneumothoraces. On chest radiographs, the nodules appear as rounded, homogenous densities 0.3 to 7.0 cm in diameter, typically located in the peripheral lung fields. They can persist unchanged, cavitate, or resolve spontaneously; frequently, they wax and wane with disease activity. Although reports attest to steroids hastening their resolution, most nodules require no specific therapy; however, a single nodule requires the same evaluation as any solitary pulmonary nodule.

Caplan's syndrome was initially described as the appearance of nodular pulmonary opacities in coal miners with simple pneumoconiosis who had symmetric polyarthritis consistent with rheumatoid disease, a positive rheumatoid factor, or both. The syndrome has subsequently been described in individuals with occupational exposure to silicates, asbestos, iron, and aluminum powder. Histologically, the nodules resemble necrobiotic nodules except that a zone of inflammatory cells containing the offending dust is interposed between the palisading epithelial cells and the central necrosis. The nodules tend to occur in crops, which may herald the onset or worsening of arthritis symptoms. Roentgenographically, the nodules are multiple, 0.5 to 5.0 cm in diameter, and peripherally located. They frequently undergo cavitation and occasionally calcify. No specific therapy currently exists.

Distal airways involvement in RA can manifest as small airways disease with expiratory airflow obstruction, bronchiectasis, bronchiolitis obliterans with organizing pneumonia (BOOP), or obliterative bronchiolitis.

Small airways disease resulting in expiratory airflow obstruction occurs in 16% to 30% of nonsmokers and 60% of smokers with RA. Airflow obstruction is caused by a peribronchiolar mononuclear cell infiltration, which can progress to an obliterative bronchiolitis. Small airways disease is associated with the presence of rheumatoid factor in

high titer, rheumatoid nodules, keratoconjunctivitis sicca (Sjögren's syndrome), and specific HLA alloantigens.

Pathologically, *BOOP* is defined as granulation tissue in terminal bronchioles with distal organizing pneumonia. The associated syndrome is associated with restrictive pulmonary function tests, cough, fever, weight loss, dyspnea, and bilateral pulmonary infiltrates. Corticosteroids are useful for treatment.

Obliterative bronchiolitis is pathologically a constrictive peribronchiolar fibrosis involving small airways; it is associated with obstructive pulmonary function tests, female gender, more advanced rheumatoid disease, use of gold and penicillamine, and Sjögren's syndrome. Rapidly progressive dyspnea with cough is seen. Corticosteroids are used in treatment.

Bronchiectasis is seen in 35% of patients on high resolution CT scan and may reflect the result of small airways disease and recurrent infections.

Specific pulmonary vascular involvement in RA is rare. Several cases of progressive pulmonary hypertension with resultant cor pulmonale have been reported in young women with long-standing RA. Although lung tissue from individuals with rheumatoid interstitial pneumonitis occasionally contains a minor component of vasculitis, lung histology from these women predominantly reveals pulmonary arteritis with fibrotic intimal proliferation and medial hypertrophy within small muscular pulmonary arteries and negligible interstitial pneumonitis. Whether such cases represent a distinct variant of rheumatoid lung disease rather than a coincidental association of pulmonary arteritis with RA remains unclear. Patients with this syndrome have a poor prognosis and look and behave similarly to those with primary pulmonary hypertension.

Pulmonary capillaritis and diffuse alveolar hemorrhage have been described but they are rare. Secondary pulmonary hypertension from interstitial pneumonitis can occur.

Apical fibrocavitary lesions have been described in a very small number of patients with RA. A recent report suggested that this is a clinically distinct pattern of lung involvement in RA. Clinically, the lesions may suggest tuberculosis and look similar to the apical pulmonary lesions seen in ankylosing spondylitis. Pathologically, cavitary necrobiotic nodules (clinically unsuspected) and interstitial fibrosis are seen.

Other pulmonary conditions seen in patients with RA include malignancies, bronchiogenic carcinoma and lymphomas, and amyloid deposition that can present with interstitial infiltrates.

Finally, be aware that rheumatoid arthritis can involve structures that can affect the upper airway. Cricoarytenoid arthritis can produce laryngeal obstruction and stridor. In addition, C1–C2 subluxation, which can occur with neck hyperextension during oral endotracheal intubation, can produce quadriparesis.

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97. THE LUNGS IN SYSTEMIC LUPUS ERYTHEMATOSUS, PROGRESSIVE SYSTEMIC SCLEROSIS AND ITS VARIANTS, POLYMYOSITIS, DERMATOMYOSITIS, AND MIXED CONNECTIVE TISSUE DISEASE

Asha Vyas Devereaux and Cecilia M. Smith

Systemic lupus erythematosus (SLE) commonly affects the lungs and pleura. Manifestations of SLE that directly affect the respiratory system include (1) pleuritis with or without pleural effusions; (2) acute lupus pneumonitis; (3) chronic interstitial pneumonitis and interstitial fibrosis; (4) hemorrhagic alveolitis with or without hemoptysis; (5) bronchiolitis obliterans with organizing pneumonia; (6) diaphragm-respiratory muscle dysfunction; (7) upper airway dysfunction; and (8) pulmonary hypertension with or without thromboembolic disease. The indirect effects of SLE on the lungs arise from predisposition to infection; in fact, pneumonia is the most frequent cause of infiltrates in patients with lupus.

Pleuritis, with or without effusions, is the most common pulmonary manifestation of SLE, occurring in 50% to 75% of patients, with a slightly higher male predominance. It can occur at any time during the clinical course and is the initial manifestation in approximately one third of cases. The effusions are generally small and bilateral but can be massive, unilateral, or associated with a pericardial effusion. The exudative fluid can be clear or serosanguinous and the pH can be high or low; however, the glucose is usually greater than 56 mg/dl, which is useful in distinguishing it from a rheumatoid effusion. Cell counts reveal predominantly polymorphonuclear cells. Total hemolytic complement and serum antinuclear antibody (ANA) titers can be high or low, but pleural fluid ANA titers greater than 1:320 strongly support the diagnosis of SLE pleuritis. Lupus erythematosus cells in the pleural fluid are diagnostic. Although most pleural effusions resolve completely with steroid therapy, some residual pleural thickening can persist.

The incidence of *interstitial pneumonitis* in SLE is controversial, dependent on whether clinical, pulmonary function testing, or histologic criteria are used. Histologic changes display a spectrum similar to idiopathic interstitial pneumonitis, ranging from interstitial mononuclear infiltration to extensive fibrosis. The presence of anti-Sm antibodies in the serum significantly correlates with lung fibrosis. Clinically, acute

lupus pneumonitis often presents with the sudden appearance of fever (as high as 104°F) and a nonproductive cough, which can progress rapidly to frank respiratory failure. Histology reveals a florid mononuclear cell infiltrate, interstitial thickening, alveolitis, and vasculitis. Several series report findings of immune complexes and complement within the alveolar walls and within the pulmonary arterioles and small vessels.

In contrast with other collagen vascular diseases such as rheumatoid arthritis and scleroderma, *chronic interstitial pneumonitis and interstitial fibrosis* is uncommon in SLE. In one report, fibrosis was observed in fewer than 3% of patients with lupus. Patients with fibrosis tend to be older (45–50 years) and have had a prolonged duration of disease before the development of chronic lung disease. The histologic findings include evidence of (1) chronic or recurrent pneumonitis; (2) interstitial and alveolar fibrosis; and (3) immunoglobulin and complement deposition in the alveolar septae. The nail fold capillary density is a useful physical finding, because it correlates with the extent of gas exchange deficiency. Both acute and chronic lupus pneumonitis may clear radiographically. However, they can also progress to advanced interstitial fibrosis and *honeycomb lung*. Even after improvement in symptoms and radiographic appearance, decreased diffusing capacity of lung for carbon monoxide (DLCO) and restrictive defects in pulmonary function often persist.

Pulmonary alveolar hemorrhage is a relatively rare presenting feature of SLE. It occurs predominantly in women and is associated with the presence of lupus nephritis. In the correct setting, the combination of anemia and hypoxemia may suggest its presence. Mortality approaches 50% and is even higher in patients who have required mechanical ventilation, have received cytoxan (perhaps indicating more advanced disease), or have a nosocomial infection. Pathology usually shows a capillaritis.

A relatively common finding in open lung biopsy specimens is *bronchiolitis obliterans with organizing pneumonia* (BOOP), which includes characteristic plugs of granulation tissue within small airways and alveolar ducts in conjunction with inflam-matory changes of the bronchioles and pulmonary parenchyma. The usual clinical presentation is nonspecific and patients show a restrictive ventilatory defect. Diagnosis requires open lung biopsy, and the pathologic changes tend to respond to steroid treatment.

Physiologic studies have recently disclosed the importance of *diaphragmatic and respiratory muscle weakness* as a cause of dyspnea and a restrictive ventilatory defect in some patients with SLE. A condition known as *shrinking lung syndrome* consists of dyspnea with chest radiograph findings of small lung volumes, elevated hemidiaphragms, and basilar atelectasis. Maximal inspiratory pressure and maximal expiratory pressure measurements demonstrate inspiratory and expiratory respiratory muscle weakness as the basis for the restrictive ventilatory defects. Comparing the movement of the two hemidiaphragms by fluoroscopy is not useful because both tend to be affected. Transdiaphragmatic pressure during active breathing, measured by esophageal and gastric balloons, confirms the presence of diaphragmatic weakness. Most patients do not have diffuse muscle weakness; therefore *random* muscle biopsy is of little utility. The pathogenesis remains unclear and the optimal therapy for this syndrome has not been established. Case reports show improvement in symptoms with β_2 agonists, steroids, or theophylline.

Although *upper airway involvement* is uncommon in SLE, hypopharyngeal ulceration, laryngeal inflammation, epiglottitis, and subglottic stenosis have been reported, which may result in complications following endotracheal intubation.

Pulmonary hypertension with cor pulmonale, which can be seen with or without associated pulmonary emboli, is significantly correlated with the antiphospholipid syndrome. In one series of 24 patients who had pulmonary hypertension, 68% had a lupus anticoagulant or cardiolipin antibody. The cause of pulmonary hypertension in SLE is controversial, and can vary among patients. Possible causes include (1) small vessel arteriopathy; (2) chronic large vessel thromboembolic disease; and (3) secondary hypertension caused by end-stage parenchymal fibrosis. In many patients, the pathologic findings in the pulmonary vascular bed are indistinguishable from primary pulmonary hypertension. Raynaud's phenomenon is almost uniformly seen in cases not associated with parenchymal lung disease. Vasculitis and immune deposits are seen in SLE with or without the development of pulmonary hypertension. On the other hand, thromboembolism occurs in up to 25% of patients with SLE and is a major cause of death. Most patients are treated with life-long anticoagulation. One case of suc-

cessful thromboendarterectomy for chronic pulmonary thrombembolic disease (PTE) in a patient with lupus was reported.

Acute reversible hypoxemia has been described in patients with lupus having normal chest radiographs and widened A-a gradients. Patients generally present with pleuritic chest pain, dyspnea, and chest discomfort. Vital capacity and DLCO are significantly reduced. The syndrome appears to respond to corticosteroids, which improve oxygenation. The cause may be transient, complement-mediated aggregation and neutrophil activation within the pulmonary vasculature. Active disease is associated with increased expression of E-selectin and vascular adhesion molecule-1 (VCAM-1), which may facilitate a leuko-occlusive vasculopathy in the lung.

Pulmonary function abnormalities are common, occurring in 70% to 80% of patients with SLE-associated lung disease even in the absence of symptoms and radiographic abnormalities. The most common abnormalities are decreased DLCO and reduced lung volumes. Airway obstruction is unusual. Hypoxemia at rest or with exercise is frequently present. Concomitant renal dysfunction is frequently seen with lupus-associated pulmonary disease.

The management of pulmonary involvement in SLE is generally supportive. Steroids appear to be the most useful drug, with other agents such as cytoxan and azathioprine added according to the severity of organ involvement. Even if the patient responds to therapy, pulmonary involvement is a poor prognostic sign; respiratory syndromes in SLE have been associated with a twofold increased risk of death at 1 year.

Progressive systemic sclerosis (PSS) or *systemic scleroderma* commonly affects the lung and pulmonary pathology is found in approximately 90% of patients at autopsy. The *CREST syndrome*, a limited variant of scleroderma, has a different spectrum of pulmonary involvement and will be discussed separately.

The age distribution and gender predominance of pulmonary involvement reflect those of PSS in general: most patients are in the fourth to sixth decades with a 3:1 female predominance. The lung is the fourth most common organ involved in scleroderma, ranking behind skin, peripheral vascular, and esophageal disease. However, pulmonary complications are the most frequent cause of death, making early detection of lung involvement an important predictor of survival. The main processes encountered include (1) interstitial fibrosis; (2) pulmonary hypertension; (3) BOOP; (4) pleuritis; (5) aspiration pneumonitis; (6) respiratory muscle dysfunction (similar to SLE); and (7) predisposition to silica-associated pneumoconiosis, sarcoidosis, and bronchogenic carcinoma.

Although the lung is commonly affected, respiratory symptoms are rarely the presenting complaint. Dyspnea on exertion is the most common pulmonary symptom, followed by a nonproductive or minimally productive cough. Pleuritic chest pain and pleural effusions are rare. Lung examination reveals basilar inspiratory crackles. Signs of pulmonary hypertension may be present. Hemoptysis is rare.

Approximately 74% of patients with the diffuse form of scleroderma develop interstitial fibrosis, which pathologically resembles idiopathic pulmonary fibrosis (IPF). The pathogenesis is unclear, but recent evidence suggests a multifactorial cause involving hyperproliferative lung fibroblasts, increased vascular permeability caused by capillary damage, and an alveolitis. As fibrosis progresses, severe pulmonary architectural distortion occurs, which is associated with bronchiectasis and the formation of cystic air spaces of up to 1 to 2 cm in diameter in a subpleural distribution. Rupture of these cysts can result in spontaneous pneumothorax. Pulmonary hypertension can also develop in association with the interstitial lung process. Radiographic evidence of fine basilar reticular or reticulonodular changes is usually accompanied by restrictive pulmonary function defects. A reduced DLCO may be the first indication of pulmonary involvement and has been found to be quite sensitive. In the absence of radiographic or ventilatory defects, significant dyspnea with a low DLCO suggests the presence of pulmonary vascular disease.

The incidence of pulmonary arterial hypertension (PAH) in scleroderma ranges from 6% to 60% depending on the study used to diagnose PAH. Isolated PAH is more common in patients with long-standing Raynaud's phenomenon and those with the limited (CREST) form of scleroderma, and correlates with physical examination findings of enlarged nailfold capillaries. Additionally, the presence of autoantibodies to antitopoisomerase 1 is associated with severe pulmonary vascular disease. The patho-

genesis of PAH consists of progressive parenchymal fibrosis and vasospasm of the pulmonary arteries. (Left ventricular failure, secondary to systemic hypotension (HTN) or cardiomyopathy, is frequently coexistent). Vascular lesions consist of proliferation, medial hyperplasia, and myxomatous changes. They occur in pulmonary arteries of all sizes, leading to pulmonary hypertension and cor pulmonale. Isolated PAH has a worse prognosis than PAH secondary to fibrosis, with a 2-year survival of 40%. Oxygen and vasodilator therapies have shown some effect on reducing pulmonary artery pressures. Many authors advocate the addition of warfarin anticoagulation, based on its apparent efficacy in the treatment of primary pulmonary hypertension. BOOP is rare. When it does occur, it presents with severe restriction and markedly decreased diffusing capacity, but responds well to high doses of prednisone.

Pleuritis is present histologically in up to 85% of patients at autopsy, but is only symptomatic in 16% of patients with scleroderma. Clinically significant effusions are uncommon. Pleural effusions or pleural thickening occur as a result of scleroderma involving the pleura or secondary to congestive heart failure from cardiac involvement. Re-expansion of the lung after thoracentesis is usually slow because of decreased lung compliance and recurrence is common, often requiring pleurodesis.

Aspiration pneumonitis can occur because of esophageal dysfunction, which can contribute to the development of chronic pneumonitis. Respiratory muscle dysfunction without generalized weakness has been reported to occur, similar to the phenomenon described in SLE. A twofold increased incidence of bronchogenic carcinoma has been observed with systemic sclerosis, relative to the normal population. Older patients, diffuse disease, presence of pulmonary fibrosis, and anti-topoisomerase 1 antibody were associated with an increase risk of cancer in scleroderma.

An association between sarcoidosis and scleroderma has been observed in clinical studies. Affected patients usually have the limited form of scleroderma, which typically precedes sarcoidosis by many years. Steroids are effective in treatment. In some instances, PSS is associated with silicosis and amyloidosis. These patients are described as having an acute onset of symptoms with predominance of pulmonary disease and, frequently, pleural effusion.

The *CREST syndrome* is a relatively *benign or limited variant of progressive systemic sclerosis*, which lacks the severe visceral organ involvement seen in more classic PSS. The syndrome consists of (1) calcinosis; (2) Raynaud's phenomenon; (3) presence or absence of esophageal dysfunction; (4) sclerodactyly; and (5) telangiectasias. However, pulmonary vascular changes similar to those in PSS are found, leading to pulmonary hypertension and cor pulmonale. Pulmonary function studies are abnormal in most patients; decreased DLCO is the most common finding, followed by reduced lung volumes and airway obstruction. Chest roentgenograms reveal interstitial infiltrates in approximately one third of patients. Isolated pulmonary hypertension without diffuse interstitial lung disease is more common in CREST than in typical PSS. In one study of 17 patients with the CREST syndrome, the incidence of pulmonary hypertension was 29%, and the development of lung carcinoma was 21%.

Antinuclear antibody typically of a speckled fluorescence is found in more than 90% of patients with scleroderma. Anti-DNA topoisomerase I (Scl-70), anti-U3 ribonucleoprotein (anti–U3-RNP), and anti-RNA polymerase I, II, and III antibodies are associated with diffuse scleroderma, whereas anticentromere antibodies (ACA) are associated with the CREST variant.

Patients who are ACA positive have been noted to have a decreased frequency of interstitial fibrosis and restrictive lung disease. On the other hand, anti–Scl-70 antibodies are associated with diffuse skin involvement, visceral organ involvement, interstitial lung disease, and a greater risk of cancer.

No therapeutic regimens exist to arrest or reverse the disease at an early stage. Most therapeutic trials have been uncontrolled and retrospective, involving patients at various stages of disease. However, a 1993 study of combined therapy with cyclophosphamide and low-dose prednisone reported an increase in the forced vital capacity after 6 months of therapy with the improvement maintained at 12, 18, and 24 months. Similar results were reported in subsequent trials. Although the clinical data have limitations, the current recommendation for progressive interstitial disease is to begin alternate-day systemic corticosteroids (prednisone 0.5 mg/kg/d) for 3 months in conjunction with cyclophosphamide (1–2 mg/kg/d) or azathioprine (1–3 mg/kg/d) based on

ideal body weight. This should then be followed by a gradual tapering of the steroid dose. In patients with indolent interstitial disease whose disease is stable, D-penicillamine or colchicine can be considered. Lung transplantation may be an option for limited scleroderma, if no other organ disease is present. Otherwise, treatment of pulmonary involvement in PSS is supportive.

Polymyositis is an inflammatory, autoimmune myopathy characterized by proximal muscle weakness. Dermatomyositis is similar to polymyositis and additionally involves the skin with a characteristic heliotrope rash. Pulmonary involvement has been reported in up to 10% of patients and is a significant cause of mortality. Both conditions have a 2:1 female predominance with a peak incidence in the fifth and sixth decades. The syndromes which are associated with polymyosis and dermatomyositis can be loosely separated into the following categories: (1) adult polymyositis; (2) adult dermatomyositis; (3) childhood polymyositis or dermatomyositis; (4) polymyositis or dermatomyositis associated with malignancy; and (5) polymyositis or dermatomyositis associated with a pre-established collagen vascular disease.

The syndrome may affect the lung in any of the following ways: (1) primary interstitial pneumonitis with progression to fibrosis; (2) pulmonary hypertension secondary to interstitial lung disease or pulmonary vascular disease; (3) recurrent aspiration pneumonitis secondary to esophageal muscle dysmotility; (4) hypoventilation, atelectasis, and pneumonia secondary to respiratory muscle weakness; and (5) BOOP.

The pulmonary component of polymyositis or dermatomyositis can precede the muscle symptoms by years. When interstitial pneumonitis precedes muscle manifestations, the diagnosis can be missed because of focus on the pulmonary disease. The presence of serum antibody to histidyl-tRNA-synthetase (anti–JO-1) significantly correlates with interstitial lung disease in up to 75% of patients. The discovery of this antibody in a patient with isolated pulmonary interstitial lung disease may be helpful in predicting the future development of polymyositis or dermatomyositis.

Two other forms of respiratory involvement can occur as complications of therapy: (1) opportunistic infection secondary to immunosuppressive drugs and (2) drug-induced lung changes secondary to cytotoxic therapy for the muscle component of the disease.

The pathologic findings differ between patients with acute, symptomatic interstitial lung disease and those with a more subacute or chronic presentation. In the acute presentation, patients may present with cough, fever, and dyspnea with or without skin or muscle findings. The chest x-ray study shows diffuse mixed alveolar interstitial infiltrates. The clinical course is similar to Hamman–Rich syndrome. Pathologic findings include an alveolitis, BOOP, or diffuse alveolar damage with focal alveolar hemorrhage. Vasculitis is not a feature of polymyositis or dermatomyositis. With the chronic presentation, pathology usually is consistent with the usual interstitial pneumonitis. The pathogenesis of the muscle and pulmonary manifestations of the disease is thought to involve T-cell activation by muscle autoantigens, resulting in a release of IL-2 and γ-interferon. Subsequent promotion of macrophages and a newly recognized cytokine called *macrophage inflammatory protein* lead to eventual tissue injury.

Clinically, respiratory symptoms are absent in up to 40% of patients with roentgenographic or histologic pulmonary changes. When symptoms occur, patients may present with dyspnea, dysphagia, or a nonproductive cough. Examination of the lungs of patients with interstitial lung disease characteristically reveals fine, late inspiratory crackles (described as *velcrolike*) in a bibasilar distribution. Roentgenographically, the disease manifests as a lower lobe reticulonodular infiltrate with an associated alveolar filling component in 20% of patients. Pleural involvement is rare. Pulmonary function studies typically show a restrictive pattern caused by either interstitial changes or respiratory muscle weakness. Commonly, a reduced DLCO is also found.

Routine laboratory findings are nonspecific. The sedimentation rate is usually elevated, whereas antinuclear antibodies and rheumatoid factor are negative. Serum levels of muscle enzymes (creatine kinase and aldolase) are elevated in most cases.

Response to therapy varies, depending on the histologic features. BOOP is most responsive to steroids, whereas diffuse alveolar damage has uniformly poor prognosis. Corticosteroids can be used alone, or in combination with cyclophosphamide or azathioprine for parenchymal lung disease.

Mixed connective tissue disease (MCTD) has clinical and laboratory characteristics of SLE, polymyositis or dermatomyositis, and scleroderma. The distinguishing feature of

MCTD is an antibody to extractable nuclear antigen, ribonuclease-sensitive ribonucleoprotein (sn-RNP). Dilutions of sn-RNP greater than 1:10,000 is considered confirmatory of MCTD.

The incidence of pulmonary involvement in MCTD is approximately 80%. Pleural effusion (25% to 50%), interstitial pneumonitis, pulmonary vasculitis, pulmonary artery hypertension, pulmonary thromboembolic disease, aspiration pneumonia, and hypoventilatory failure can occur. Presenting symptoms include exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever. Clubbing is not seen. One third of patients are asymptomatic; however, 75% of them will have evidence of pulmonary involvement on chest x-ray study or pulmonary function studies. A correlation with HLA-DR3 and interstitial lung fibrosis has been observed in one small study.

Histopathology of the lung in interstitial lung disease associated with MCTD is similar to IPF. Additionally, a proliferative vasculopathy is associated with MCTD, characterized by intimal thickening with medial muscular hypertrophy of the pulmonary arteries and arterioles, which correlates with the presence of pulmonary hypertension.

Radiographically, bilateral basilar interstitial opacities, right ventricular hypertrophy, and pulmonary artery enlargement can be seen. Pulmonary function abnormalities include decreased DLCO (up to 67% of patients) and reduced lung volumes (50% of patients). Small airway obstruction is seen early and is an indication of functional impairment.

It had been reported that the pulmonary disease of MCTD is benign and responds to steroid therapy with improvement shown on the chest roentgenogram and pulmonary function studies. A few reports, however, describe progressive pulmonary disease and rapid deterioration despite steroid therapy. Renal disease and Raynaud's phenomenon is associated with a higher mortality rate. Some long-term, follow-up studies show evolution of MCTD toward other connective tissue diseases (SLE, PSS, and rheumatoid arthritis). The overall prognosis is estimated to be similar to that seen in patients with SLE.

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98. EOSINOPHILIC GRANULOMA

Suzanne J. Timmer and Cecilia M. Smith

Eosinophilic granuloma (EG) or primary pulmonary histiocytosis X, is one entity in a spectrum of diseases of unknown cause that all involve proliferation of the histocytosis X cell. The other diseases in this group include Letterer–Siwe disease and Hand-Schüller-Christian disease. The latter two diseases have characteristic ages of onset, are more severe, and affect multiple organs including bone and occasionally soft tissues with an infiltration of atypical histocytes. Although eosinophilic granuloma was initially described as a disease of bone, more than 20% of cases have a pulmonary component. In many cases, the lung is the only site of involvement. Some researchers view histiocytosis X as an abnormal proliferative condition, localized or disseminated, in which the stem cells emanate from the Langerhans' cell system.

Eosinophilic granuloma can occur at any age and has been reported as early as infancy (3 months of age) and up to the seventh decade. However, the onset of disease is most common in ages 20 to 40 years. Clinical series reported conflicting results on the presence of gender predominance. No familial or ethnic associations appear to exist. Smoking appears to be a risk factor for developing pulmonary histiocytosis X; more than 90% of patients have a positive smoking history.

Patients may present without any symptoms (23% in one series), focal respiratory symptoms (cough, dyspnea), or vague constitutional symptoms (fever, malaise, and

weight loss). Pneumothorax is a characteristic manifestation (15% in one series), especially in young men. Chest pain is less common as a presenting complaint; it can be caused by pneumothorax or lytic rib lesions. Hemoptysis and wheezing are rarely seen. Atypical presentations include an endobronchial lesion presenting with atelectasis, solitary pulmonary nodule, pleural effusions, hilar and mediastinal lymphadenopathy, and an anterior mediastinal mass without parenchymal involvement. Diabetes insipidus is seen in a small number of these patients (5%). The physical examination can be completely normal. Rales are noted in 20% of patients; decreased breath sounds and wheezes are less common.

The diagnosis of EG is suggested when a young (aged 20 or 30 years) man or woman presents with chest x-ray findings of an interstitial process that predominantly affects the upper lung zones. The diagnosis is more likely if bone lesions are also present. The parenchymal abnormalities include nodules of various sizes (1–10 mm), interstitial linear markings, cysts, and bullae. Typically, no hilar node enlargement is seen. High-resolution computed tomography (HRCT) of the chest is recommended to delineate distribution of cysts, bullae, and nodules. HRCT may predict which lesions improve. Recent data suggest that nodular opacities, thick-walled cysts, and ground glass opacities regress; in contrast, thin-walled cysts, linear opacities, and emphysematous lesions progress or do not change. Cases have been reported of children presenting with anterior mediastinal masses but pleural effusions are rare. Involvement of the hypothalamus, skin, and lymph nodes can occur.

Open lung biopsy is the definitive method for making a diagnosis. Stellate-shaped granulomas are typically observed under light microscopy with hematoxylin and eosin stain. These granulomas consist predominantly of histiocytes and eosinophils. The histiocyte is a large mononuclear cell with a convoluted, indented nucleus and abundant eosinophilic cytoplasm. By electron microscopy, the X-bodies and Birbeck granules are visualized within the histiocyte. These cytoplasmic bodies are considered specific for histiocytosis X cells. Immunohistochemical staining methods also can identify the histiocytosis X cell. Cell markers identifying the histiocytosis X cell include S-100 protein, sialylated *Leu*-M1 antigen, and the cell surface receptor for the monoclonal antibody OKT6. These cells, however, do not synthesize lysozyme. The cellular protein S-100 has been found in the cytoplasm and nucleus of these cells. Anti-*Leu*-M1 is effective in detecting Hodgkin's (Reed–Sternberg) cells and lymphocyte and histiocyte variants; however, staining with this antibody occurs only if the tissue section is first treated with neuraminidase for removal of sialic acid residues, a phenomenon also observed in Langerhans' cells. By using OKT6 monoclonal antibody, Langerhans' cells and histiocytosis X cells can be identified. The staining pattern of histiocytosis X cells is distinctly different from that of typical histiocytes. The benefit of identifying S-100 protein or *Leu*-M1 antigen by immunohistochemical staining is that it can identify the histiocytosis X cell from routine, formalin-fixed, and paraffin-embedded tissue. Electron microscopic analysis and monoclonal antibody markers require fresh or frozen tissue.

In most cases, the history, chest x-ray study, HRCT scan, and histology are adequate for diagnosis. However, in some cases, especially in more advanced disease with fibrosis, electron microscopic examination can discern the cytoplasmic Birbeck granules, which confirm a diagnosis. It is suggested that immunostaining with S-100 and OKT6 can be performed, in lieu of electron microscopy, to confirm the diagnosis. No one immunohistochemical staining method is superior to the others; using more than one marker increases the specificity. Positive S-100 protein staining has been seen in other diseases (e.g., infectious granulomatous diseases, interstitial lung diseases). Older lesions can be devoid of eosinophils and have only rare histiocytes present. Destruction of the normal tissue architecture leads to cyst formation and nonspecific honeycombing.

Recent reports describe the diagnosis of EG definitively by use of bronchoalveolar lavage (BAL). Electron microscopic analyses of BAL cells demonstrate specific X bodies within the histiocytosis X cells. The staining of cells obtained by BAL for S-100 protein and OKT6 has also been positive. Transbronchial lung biopsies have also disclosed the histiocytosis X cells by electron microscopic analysis. However, a negative transbronchial lung biopsy should not exclude the diagnosis of EG as sampling error can occur (i.e., a false-negative finding).

Other laboratory tests are generally not helpful. Peripheral eosinophilia is not associated with EG. Leukocytosis may be found, but generally all tests are normal. Pulmonary

function testing reveals a spectrum of abnormalities from normal to a restrictive defect, an obstructive defect, or a combination of both. The diffusing capacity of lung for carbon monoxide (DLCO) may be decreased, with evidence of hypoxemia and a widened alveolar-arterial oxygen tension difference ($P[A\text{-}a]O_2$) at rest, with exercise, or both.

In addition to the pulmonary aspects of this disease, it is recommended that a bone scan be done to identify bone lesions. Lytic bone lesions (which heal with sclerosis) appear in approximately 5% to 10% of patients with lung disease. If diabetes insipidus is suspected, a water deprivation test will confirm the diagnosis. The most common complication is recurrent spontaneous pneumothorax, occurring in 10% to 30% of cases. Hemoptysis is rare. Progression to severe pulmonary fibrosis with pulmonary hypertension and cor pulmonale is the most serious complication.

The efficacy of therapy is unknown. Smoking cessation is the first line of treatment. Fortunately, the disease is self-limited in most patients with this intervention alone. Reports on therapeutic outcomes for other patients are anecdotal. Previously, several modalities have been used, including irradiation, antibiotics, steroids, and cytotoxic drugs. Currently, no role is seen for irradiation or cytotoxic drugs. Steroids are associated with resolution of systemic symptoms and clearing of the nodular shadows on chest films. Although no controlled trial has substantiated steroid efficacy, it is generally accepted that steroids should be used if a patient's condition is deteriorating. If isolated bony lesions are present, curettage or local radiotherapy is recommended. If pneumothoraces recur, pleurodesis can be considered. Lung transplantation is a therapeutic alternative when progressive pulmonary deterioration occurs. A case of EG recurring after lung transplantation and responding to cytoxic therapy has been reported. This suggests that the primary abnormality in EG may be in the precursor dendritic cell.

The course of this disease is unpredictable. The spectrum can range from a rapid deterioration to spontaneous, complete remission. The mortality rate is reported as 2% to 6%. The presence of bone lesions associated with primary pulmonary histiocytosis X does not change the prognosis.

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2. Chollet S, et al. Diagnosis of pulmonary histiocytosis X by immunodetection of Langerhans' cells in bronchoalveolar lavage fluid. *Am J Pathol* 1984;115:225.

   Cells from BAL of 131 patients were analyzed for the presence of OKT6 reactive cells and Birbeck granules by electron microscopy. All 18 patients with pulmonary histiocytosis X stained positively with OKT6 and had granules present. Of patients, 43 with sarcoidosis, 3 controls, and 61 of 67 with miscellaneous disorders had less than 1% labeled cells (6 stained positively with OKT6 but did not contain the Birbeck granules). Histiocytosis X cells can be identified unequivocally only by transmission electron microscopy.
3. Colby TV, Lombard C. Histiocytosis X in the lung. *Hum Pathol* 1983;14:847.

   Histologic and clinical features of the disease are discussed. Describes the progression of the histologic lesions.
4. Egan TM, et al. Single lung transplantation for eosinophilic granulomatosis. *South Med J* 1992;85:551.

   A case report describing functional outcome of a 26-year-old woman who underwent single lung transplantation.
5. Flint A, et al. Pulmonary histiocytosis X: immunoperoxidase staining for HLA-DR antigen and S-100 protein. *Arch Pathol Lab Med* 1986;110:930.

   Evaluated S-100 staining in eosinophilic granuloma, idiopathic pulmonary fibrosis, and hypersensitivity pneumonitis. Positive staining for S-100 protein is not specific for histiocytosis X cells.

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10. Marcy TW, Reynolds HY. Pulmonary histiocytosis X. *Lung* 1985;163:129.
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11. Massachusetts General Hospital Case Records. Weekly clinicopathological exercises: Case 1-1992. A 34-year-old woman with dyspnea and multiple small cystic areas in the lungs. *N Engl J Med* 1992;326:44.
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A discussion of diffuse interstitial lung disease with a differential diagnosis based on the distribution of the lung disease on chest x-ray film and cystic lesions seen on HRCT scan. The clinical findings of EG are reviewed.
13. O'Donnell AE, et al. Endobronchial eosinophilic granuloma: a rare cause of total lung atelectasis. *American Review of Respiratory Diseases* 1987;136:1478.
A case report of a rare presentation of endobronchial disease.
14. Pomeranz SJ, Proto AV. Histiocytosis X: unusual-confusing features of eosinophilic granuloma. *Chest* 1986;89:88.
Seven cases of pulmonary histiocytosis X are discussed, highlighting the atypical chest x-ray findings.
15. Potente G, Bellelli A, Nardis P. Specific diagnosis by CT and HRCT in six chronic lung diseases. *Comput Med Imaging Graph* 1992;16:277.
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16. Santamaria M, et al. Expression of sialylated Leu-M1 antigen in histiocytosis X. *Am J Clin Pathol* 1988;89:211.
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17. Soler P, et al. Immunocytochemical characterization of pulmonary histiocytosis X cells in lung biopsies. *Am J Pathol* 1985;118:439.

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18. Soler P, et al. Pulmonary Langerhans' cell granulomatosis (histocytosis X). *Annu Rev Med* 1992;43:105.

A discussion of advances regarding Langerhans' cells and their role in the pathogenesis of EG. Clinical features and pathologic lesions are also described.

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Focal and diffuse air trapping during exhalation in the thin-walled cysts associated with EG is demonstrated and correlated with pulmonary function test results.

20. Tomashefski JF, Khiyami A, Kleinerman J. Neoplasms associated with pulmonary eosinophilic granuloma. *Arch Pathol Lab Med* 1991;115:499.

Describes the prevalence of pulmonary and extrapulmonary neoplasms seen in patients with pulmonary EG. Of 21 patients, 10 (48%) had benign (1 patient) or malignant (9 patients) neoplasms.

21. Travis WD, et al. Pulmonary Langerhans' cell granulomatosis (histiocytosis X): a clinicopathologic study of 48 cases. *Am J Surg Pathol* 1993;17:971.

A total of 48 patients with EG were studied to assess the usefulness of immunochemistry, electron microscopy, and HRCT scan in diagnosing this disease. The combination of characteristic findings by HRCT, in association with tissue biopsy findings, Birbeck granules by electron microscopy, or positive immunohistochemical staining for antibody to S-100 protein, supported the diagnosis.

22. Bonelli FS, et al. Accuracy of high-resolution CT in diagnosing lung diseases. *AJR* 1998;170:1507.

A retrospective review of HRCT findings in patients with pathologically proved EG (10 patients), pulmonary lymphangiomyomatosis (9 patients), and emphysema (10 patients) and controls (5) without cystic air spaces was conducted by two thoracic radiologists who were blinded to the pathologic diagnosis of the patients. When confident, the radiologists were correct 100% of the time. Patients with EG had nodules in the intervening lung parenchyma, unlike those with lymphangiomyomatosis whose lung parenchyma lacked nodules.

23. Brauner MW, et al. Pulmonary Langerhans' cell histiocytosis: evolution of lesions on CT scan. *Radiology* 1997;204:497.

Initial and final CT scans of 21 patients (11 with histologic diagnosis) with EG and CT evidence of pulmonary disease were compared retrospectively. Nodular opacities, thick-walled cysts, and ground glass opacities underwent regression. Thin-walled cysts, linear opacities, and emphysematous lesions remained unchanged or progressed.

24. Asakura S, Colby TV, Limper AH. Tissue localization of transforming growth factor-beta 1 in pulmonary eosinophillic granuloma. *Am J Respir Crit Care Med* 1996; 154:1525.

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25. Youkeles LH, et. al. Decreased tobacco-glycoprotein-induced lymphocyte proliferation in vitro in pulmonary eosinophillic granuloma. *Am J Respir Crit Care Med* 1995;151:145.

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26. Shijubo N, et. al. Eosinophilic cationic protein in chronic eosinophilic pneumonia and eosinophilic granuloma. *Chest* 1994;106:1481.

Measured eosinophilic cationic protein (ECP) in BAL fluid from patients with EG, chronic eosinophilc pneumonia, and normal controls. ECP concentration in peripheral circulation was increased both in patients with eosinophilic granuloma and in those with chronic eosinophilic pneumonia compared with controls. Chronic eosinophilic pneumonia patients had prominently increased ECP concentrations in BAL fluids compared with those found in controls, whereas patients with EG did not.

27. Archer TP, Qualman SJ, Mazzaferri EL. Chest pain and dyspnea in a 17-year-old smoker. *Hosp Pract* (Off Ed) 1998;33:94.

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28. Minghini A, Trogdon SD. Recurrent spontaneous pneumothorax in pulmonary histiocytosis X. *Am Surg* 1998;64:1040.

    A case report of a 25-year-old male smoker with previous spontaneous pneumothorax who was successfully treated with thoracoscopic stapling of bullae and pleural abrasion for recurrent disease.

29. Ten Velde GP, et al. A solitary pulmonary nodule due to eosinophilc granuloma. *Eur Respir J* 1994;7:1539.

    Presents a case report of a 42-year-old male smoker with an asymptomatic 8-mm pulmonary nodule and normal spirometry. The patient underwent thoracoscopic wedge resection and was found to have EG after electron microscopic examination of the specimen showed Birbeck granules. The patient had not developed any further lesions at follow-up visits.

30. Gabbay E, et al. Recurrence of Langerhans' cell granulomatosis following lung transplantation. *Thorax* 1998;53:322.

    A case report of pulmonary Langerhans' cell granulomatosis that recurred following lung transplantation and responded to cyclophosphamide.

31. Mitra AG, Turpin SV, Cefalo RC. Pregnancy in a patient with eosinophilic granulomatosis of the lung: a case report. *Obstet Gynecol* 1994;83:811.

    A 33-year-old ex-smoker was diagnosed with EG of the lung and treated with steroids and oxygen. The patient's pregnancy was complicated by fetal growth retardation and oligohydramnios, but resulted in delivery of a healthy infant. Her lung disease remained stable during the pregnancy on her prior therapy.

99. NEUROFIBROMATOSIS, LYMPHANGIOMYOMATOSIS, AND TUBEROUS SCLEROSIS

John Scott Parrish and Cecilia M. Smith

Neurofibromatosis type 1 (NF1, von Recklinghausen's disease) is characterized by cutaneous neurofibromas, café au lait spots, Lisch nodules of the iris, and various other systemic manifestations. Von Recklinghausen's disease, an autosomal dominant disorder, appears in all races, with a prevalence of 1 of 3000 live births. The NF1 gene is located on chromosome 17. Interstitial pneumonitis occurs in 7% to 20% of adults with NF1. Onset of interstitial pneumonitis characteristically occurs in the third or fourth decade. The cause of the pneumonitis remains obscure. Pathologically, it is grossly and microscopically indistinguishable from the idiopathic interstitial pneumonitis. The lung surface is often studded with bullae of varying sizes with a striking upper lobe predominance; a honeycombed appearance is common on sectioning. Microscopically is seen diffuse interstitial fibrosis and architectural diaruption, with extensive alveolar destruction and cystic changes. Hyperplasia of neurolemma cells of intrapulmonary nerves has been described.

Dyspnea of insidious onset is often the presenting manifestation, although discovery in an asymptomatic individual through an incidental chest roentgenogram may occur. The chest film may initially reveal only accentuated interstitial markings or diffusely mottled ill-defined soft infiltrates. The infiltrate usually progresses over years to a coarse linear or reticulated pattern and bulla formation. Interstitial fibrosis is usually symmetric with a basal predominance. Bullae form the hallmark of neurofibromatosis; the most prominent are apical or subapical. In addition to the diffuse fibrobullous interstitial disease, other thoracic manifestations of this disease include paravertebral neurofibroma, lateral meningocele, kyphoscoliotic vertebral deformity, and cutaneous neurofibroma. Physiologic measurements reveal a combination of restrictive and obstructive defects, diminished carbon monoxide diffusing capacity (D_{LCO}), and hypoxemia (initially limited to exercise).

The diagnosis is generally obvious because the neurocutaneous manifestations almost invariably precede the interstitial pneumonitis. Rarely, biopsy is necessary to exclude another infiltrative pulmonary process. The course is variable and often slowly progressive. Some patients develop respiratory failure, cor pulmonale secondary, or both to progressive pulmonary hypertension. No specific therapy currently exists.

Other thoracic manifestations include severe scoliosis and neurofibromas of the posterior or superior mediastinum. Neurofibromas arise from nerve sheaths in the sympathetic chain, vagus, and intercostal and intrapulmonary nerves. These tumors are commonly found adjacent to the spinal column. Neurogenic tumors involving the lung are rare, although multiple neurofibromas of varying size can occur. Hypoxemia can be caused by right-to-left shunts within these tumors. These tumors are usually benign, but malignant change can occur. The development of carcinoma can be a complication of the diffuse interstitial disease.

Lymphangioleiomyomatosis or lymphangiomatosis (LAM) is a rare, progressive pulmonary disorder characterized by a hamartomatous proliferation of smooth muscle within the lungs. LAM frequently involves other organs (e.g., the kidneys, retroperitoneal lymph nodes, liver, uterus, and pancreas) in addition to the lungs. Renal angiomyolipomas have been reported in 15% to 60% of patients with LAM.

Lymphangiomatosis occurs almost exclusively in women of childbearing age, in whom it can progress rapidly or slowly to respiratory failure and death. The cause of LAM is unknown. Its incidence in young women, exacerbations during pregnancy, and associated steroid receptors in the lung, coupled with the known effect of estrogen and progesterone on smooth muscle, suggest that hormonal interactions are important in its pathogenesis.

Pathologically, nodular and tortuous masses of smooth muscle cells without significant fibrosis are the hallmarks of LAM. Grossly, the pleura is thickened, and large thick-walled cystic airspaces give rise to a honeycombed appearance of the lungs. Hilar, mediastinal, and retroperitoneal lymph nodes are often enlarged and spongy, and the thoracic duct distended with lymph. Chylothorax can be present because of lymphatic rupture. Microscopically, a striking nodular proliferation of smooth muscle is seen within the pleura and alveolar walls, as well as in and around the walls of bronchioles, venules, and lymphatics. The smooth muscle cells exhibit melanoma-related marker, HMB45 immunoreactivity, distinct from other smooth muscle proliferations. HMB45, a monoclonal antibody, will also react with angiomyolipomas, clear cell tumors of the lung, and melanoma cells.

Bronchiolar obstruction from the smooth muscle proliferation leads to air trapping, resulting in destruction of alveolar septa and honeycombed cystic spaces, especially at the lung bases. Ultrastructural studies of lung biopsy specimens demonstrated degradation of elastic fibers in areas of smooth muscle accumulation, which can be a factor leading to the development of emphysematous changes. Venous obstruction results in dilation and rupture of venules, chronic low-grade hemorrhage, and, ultimately, hemosiderosis. Both estrogen and progesterone cell-surface receptors have been demonstrated in the lung.

Clinically, patients with LAM present most commonly with dyspnea or pneumothorax. Symptoms and signs reported during the course of LAM in a recent series included dyspnea (83%), pneumothorax (69%), cough (66%), chylothorax (23%), hemoptysis (20%), ascites (11%), pericardial effusion (6%), chyloptysis (3%), and chyluria (3%). With abdominal lymphatic obstruction, chylous ascites can develop. Occasionally, com-

munications form between dilated retroperitoneal lymphatics and a kidney or ureter, resulting in chyluria. Patients presenting with angiomyolipoma and pulmonary symptoms should be evaluated for LAM by chest computed tomography (CT) scan, because the two are associated.

The physical examination frequently is not revealing until late in the clinical course, when end-inspiratory rales, diminished lower lobe breath sounds, scattered rhonchi, and signs of pleural effusion are present. An abrupt exacerbation of dyspnea may signal the development of pneumothorax.

The chest roentgenogram initially may be normal, but later shows reticulonodular infiltration, with or without frank honeycombing. Occasionally, small cysts coalesce to form large blebs. This occurs predominantly at the lung bases. Unlike other forms of interstitial lung disease, in LAM the lungs often appear hyperinflated rather than small. CT scan of the chest is more accurate than the chest film in defining the presence and extent of cysts. CT demonstrates numerous thin-walled cysts throughout both lungs. Greater morphologic and physiologic correlation is seen with the CT scan than with the chest radiograph.

Laboratory findings are nonspecific except for chyluria. Pulmonary function tests (PFTs) show mild to severe obstruction superimposed on a restrictive pattern. A bronchodilator response is present in 26% of patients. Hypoxemia (worsened by exertion), reduced flows and D_{LCO} or carbon monoxide diffusing capacity, and progressive increase in plethysmographic lung volume are characteristic. Significant functional impairment usually precedes any radiographic abnormality (other than pneumothorax). Diminished exercise capacity is most likely caused by ventilatory limitation.

The radiographic distribution and character of the lesions are highly characteristic, but biopsy is necessary to confirm the diagnosis. Of 75 lung specimens obtained by transbronchial and open lung biopsy, only LAM showed HMB45-positive cells. It is suggested that if only a transbronchial biopsy is available, this marker can assist in confirming the diagnosis.

The differential diagnosis includes idiopathic interstitial pneumonitis, sarcoidosis, eosinophilic granuloma, and pulmonary hemosiderosis. Low-grade sarcomas metastatic to the lung have been rarely misdiagnosed as LAM.

The mediastinal and pulmonary lymphangiomyomas are radioresistant. Surgical or chemical obliteration (pleurodesis) of the pleural space may be necessary in patients with recurrent effusion or pneumothorax. Symptomatic therapy for bronchospasm or cor pulmonale may be required. Corticosteroids and cytotoxic agents appear to offer no benefit. Hormonal manipulation can affect muscle proliferation in this disease. Pregnancy and estrogen therapy can worsen the disease, and remission of the disease can occur after menopause. Oophorectomy or tamoxifen with progesterone therapy (or both) has been successful in some cases.

The most consistent improvement has occurred with progesterone therapy. Functional impairment can be arrested, or even reversed, if such treatment is begun before destructive changes are advanced. It is unclear why some patients respond to hormonal manipulation and others do not. It may be that the presence of advanced disease limits response at the time therapy is instituted.

Lung transplantation is a viable alternative for patients with end-stage disease. Criteria for transplantation include (1) progression despite medical therapy; (2) severe functional defects (e.g. forced expiratory volume in 1 second/forced vital capacity [FEV_1/FVC] < 50%, total lung capacity > 130%, FEV_1 < 30%); and (3) severe cystic disease on high resolution CT (HRCT). Recurrence of LAM in the transplanted lung has been reported.

Patients with extensive cystic changes and hyperinflation usually survive only 3 to 10 years following the onset of symptoms. A few with primarily mediastinal LAM with minimal parenchymal involvement survive longer.

Tuberous sclerosis is an autosomal dominant, hereditary, neurocutaneous disease. It has a broader systemic constellation of complications than LAM, but the pulmonary component of this disease appears identical to that in LAM. A controversy exists regarding whether LAM is a *forme fruste* of tuberous sclerosis.

Lung involvement in tuberous sclerosis occurs principally in young women of childbearing age; dyspnea rapidly worsens, and cor pulmonale develops within years of its

onset. This differs from classic tuberous sclerosis, in which no gender predilection is seen. Pregnancy exacerbates both diseases. Both disorders are associated with renal angiofibrolipomatous tumors.

Tuberous sclerosis is a rare disease, occurring in 1 in 100,000 to 170,000 people in the general population. Two genes responsible for tuberous sclerosis (TSC1, TSC2) have been identified on chromosomes 9 and 16. The classic triad in this disease includes mental retardation, seizures, and dermal angiofibroma (adenoma sebaceum). The clinical features, however, can vary. Patients' intelligence is normal. The primary features of tuberous sclerosis complex (TSC) have been described to be central nervous system (CNS) lesions of cortical and subependymal tubers, ungal fibromas, and facial angiofibromas (sebaceous adenomas). Secondary lesions include Shagreen patches, cerebral tubers, retinal hamartomas, multiple renal tumors, sclerotic bone lesions, and cardiac rhabdomyomas.

Pulmonary involvement in tuberous sclerosis is rare, occurring in approximately 1% to 2% of patients. Pulmonary manifestations appear later than the cutaneous and neurologic ones. When pulmonary disease is manifested, it occurs most often in women of childbearing age without any CNS disease. When pulmonary disease is present, it usually dominates the clinical picture and can be the cause of death from either cor pulmonale or pneumothorax. (However, the most common cause of death is renal disease.) Lymph node involvement and chylous effusions are reported, but rarely. Pneumothorax and pulmonary insufficiency are common. Exertional dyspnea is the major symptom. Chronic cough and hemoptysis occur frequently. Lung histology, chest radiographic and CT scan findings, pulmonary presentation, and clinical course are similar to LAM.

In suspected cases, thorough cutaneous and ophthalmologic examinations should be performed. The diagnostic workup should include cranial CT scan, renal ultrasound, and skeletal radiographs in addition to chest x-ray study, chest high-resolution CT (HRCT) scan, and pulmonary physiology studies. A rare but early indicator of tuberous sclerosis is an unusual but characteristically expanded, dense rib deformity. These bony lesions can be mistaken for fibrous dysplasia or Paget's disease.

Estrogen receptors have been demonstrated in the lungs of patients with TSC. Tamoxifen and progesterone therapy have slowed the pulmonary disease in tuberous sclerosis, similar to descriptions for LAM. Genetic counseling is an important component in the management of patients with this disease.

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100. PULMONARY ALVEOLAR PROTEINOSIS

Angela C. Wang

Pulmonary alveolar proteinosis (PAP) is composed of a rare group of congenital and acquired diseases characterized by the deposition within alveoli and airways of large amounts of eosinophilic material rich in lipids and protein, such as surfactant. The peak age of onset is between 30 and 60 years; however, the disease has been described in all ages. Congenital forms of PAP exist and are associated with surfactant gene defects. In adults, the male:female ratio is approximately 3:1. Most patients are current or previous smokers.

Primary PAP occurs in the absence of an identifiable associated disease or exposure. Three main groups of *secondary* PAP have been identified: (1) lung infections, (recently alveolar proteinosis has been demonstrated in *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS) and without AIDS); (2) hematologic malignancies and other immune altering conditions; and (3) exposure to inhaled chemicals and minerals. A number of toxic insults to the lung (silica, NO_2, ozone, and $ONOO^-$) can result in alveolar proteinosis. PAP has also been produced in laboratory animals by inhalation of inert dusts of extremely fine particulate matter. However, no consistent environmental or occupational associations have been uncovered in patients with alveolar proteinosis. Whether primary alveolar proteinosis is an entity distinct from proteinosis associated with other diseases is not clear. Although the two forms are similar histologically, subtle differences may exist.

The cause of PAP is unknown, but is believed to involve the disrupted clearance and catabolism of surfactant by alveolar macrophages. Mice that do not express granulocyte-macrophage colony stimulating factor (GM-CSF) or in which function of the GM-CSF receptor has been disrupted accumulate excessive levels of alveolar surfactant substances similar to that seen in human patients. The role of GM-CSF in the pathogenesis of both forms of human PAP remains to be fully elucidated. It has been suggested that secondary PAP represents a reaction to a particular form of lung injury. Dysregulation of inflammatory cell activity could result in disruption of surfactant recycling.

Although PAP most commonly presents insidiously, an abrupt onset can occur that is associated with a concomitant respiratory infection. Some patients are asymptomatic at the time of diagnosis; however, most patients present with some degree of dyspnea and cough. Sputum production is usually scant but on occasion has been described as containing small *chunks* of material. Other much less common symptoms include weight loss, weakness, chest pain, and hemoptysis. Physical findings, if present, are nonspecific. Fever usually implies superinfection, although a low-grade fever is occasionally present. Rales occur in a few patients; in severe cases, cyanosis and clubbing are observed. The most common laboratory finding is a mildly elevated serum lactate dehydrogenase. Patients with severe disease may have secondary polycythemia. The leukocyte count is normal or slightly increased. Serum protein electrophoresis may reveal increased globulins. Recently, serum levels of lung surfactant proteins A and D (SP-A and SP-D) have been found to be markedly elevated in patients with PAP compared with normal volunteers. Increased levels of these two proteins were also found in patients with idiopathic pulmonary fibrosis. In contrast, patients with interstitial pneumonia associated with various collagen-vascular diseases were found to have an elevated

serum SP-D, but not SP-A. Pulmonary function tests reveal a restrictive pattern with decreased static lung compliance and decreased carbon monoxide diffusing capacity. Arterial blood gases demonstrate hypoxemia and a widened alveolar-arterial oxygen gradient. Chest radiographs typically show diffuse, finely nodular, soft infiltrates in a perihilar *butterfly* pattern, similar in appearance to pulmonary edema; however, other signs of left ventricular failure (cardiomegaly, Kerley B lines) are absent. A miliary, interstitial, or multinodular pattern and lobar consolidation can also be seen. Hilar adeno-pathy, pleural effusions, and cavitation are rare and suggest superimposed infection. Findings on high resolution computed tomography (HRCT) scanning, although not pathognomonic, can be strongly suggestive of PAP and may demonstrate the extent and pattern of PAP more clearly than plain radiographs. The presence of the phospholipid or proteinaceous material within alveoli correlates with a *ground glass* appearance. Intralobular and interlobular septa are typically thickened, often in polygonal patterns termed *crazy-paving*.

The differential diagnosis includes any disease that can produce a diffuse acinar-filling pattern on chest roentgenogram, including cardiogenic and noncardiogenic pulmonary edema, toxic inhalations, pulmonary hemorrhage, viral pneumonia, and *P. carinii* infection. One of the clues to the diagnosis of PAP is the disparity between extensive radiographic abnormalities and the minimal clinical symptomatology. When chest roentgenograms reveal a predominant interstitial pattern, the diagnosis becomes more difficult. Although open lung biopsy has been thought of as the *gold standard* for diagnosing PAP, bronchoscopy with transbronchial biopsy has a high rate of success. Bronchoalveolar lavage (BAL) is becoming increasingly useful. Typically, the BAL fluid in PAP appears opaque and milky. Microscopically, diffuse eosinophilic staining, large eosinolphilic bodies, and few alveolar macrophages are seen. Both SP-A and SP-D levels are elevated in BAL fluid obtained from patients with PAP and may prove helpful in distinguishing this disease from other diffuse lung disorders.

The course of PAP is variable. Before 1970, the mortality rate was approximately 30%, either from the disease itself or from a complicating superinfection. Approximately 25% of patients had complete or near-complete resolution without bronchopulmonary lavage. In contrast, two recent series suggested mortality rates of 8.8% and 0 in long-term follow-up. The prognosis in infants remains grave, however, with few surviving beyond 2 years after diagnosis.

The major complication of PAP is infection. Alveolar macrophage function is impaired in this disease, perhaps because of an inhibiting protein found in the lavage fluid. Bacterial, mycobacterial, and fungal infections have been reported frequently; often, exacerbations of the disease respond to antibiotics without a definite bacteriologic diagnosis. *Nocardia asteroides*, and *Mycobacterium tuberculosis* have appeared most often in case reports. In one large series, *M. avium-intracellulare* was isolated from lavage fluid in 42% of cases. Other complications include pulmonary fibrosis, cor pulmonale, and spontaneous pneumothorax.

Whole lung lavage remains the only consistently successful treatment for PAP. However, the possibility of spontaneous resolution of PAP has made clinical decision-making regarding the need for and frequency of whole-lung lavage less clear. In one series from the Cleveland Clinic, 46% followed over a prolonged period never required whole lung lavage. Another 29% required repeated whole lung lavage for recurring signs and symptoms of PAP. Because of the rarity of PAP, only a few referral centers have developed extensive experience in whole lung lavage. In general, the indications for whole lung lavage are dyspnea or hypoxemia. Radiographic evidence alone is probably not sufficient to warrant the procedure.

Pulmonary segmental flooding (lavage) by an endobronchial catheter or fiberoptic bronchoscope has been successful in clearing radiographic infiltrates. Placement of a Carlens tube allows ventilation of one lung with 100% oxygen, while the other lung is irrigated with 10 to 20 L of saline. If oxygen saturation does not reach satisfactory levels in 3 to 4 days, the procedure can be repeated. Improvement in gas exchange, pulmonary function tests, symptoms, and radiographic infiltrates occurs in approximately 80% of patients following lavage. Complications include hypotension during the irrigation phase and hypoxemia and carbon dioxide retention following lavage, caused by spillage into the ventilated lung or to postlavage ventilation-perfusion alterations in the lavaged and nonlavaged lungs.

Treatment for PAP has also included corticosteroids, supersaturated potassium iodide solution, and aerosolized and oral proteolytic agents. None of these treatments have been shown to be clearly beneficial and some may be detrimental. For instance, corticosteroids are relatively contraindicated because of the high incidence of associated infection. Potential adjunct or even alternative therapies include aerosolized or systemic GM-CSF. Given the evidence for defective GM-CSF signaling in mice and some humans with PAP, lung transplantation should not be performed until this form of PAP has been ruled out, because the disease can recur. The possibility of bone marrow transplantation should be considered as potentially curative treatment for these patients.

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101. LUNG IN IMMUNOCOMPROMISED HOSTS

Stephen W. Crawford

Immunosuppressed patients are more susceptible to pulmonary infection because of compromised (1) granulocyte number and function; (2) immune function (i.e., lymphocyte activity); (3) mechanical barriers to colonization and infection; and (4) exposure to pathogens.

Bacterial pneumonia is the most common cause of focal pulmonary infiltrates in patients with the acquired immunodeficiency syndrome (AIDS) and with leukemia, either before or during chemotherapy. The primary risk factor for infection is neutropenia. The clinical presentation of bacterial pneumonia is similar to that seen in patients with normal immune systems. Fever, tachypnea, focal radiographic infiltrates, and cough are common. However, sputum production may be scant because of granulocytopenia. Typical organisms are similar to those affecting the general population. *Pneumococcus*, *Hemophilus*, and other community-acquired organisms are common, as are gram-negative bacteria. Encapsulated gram-positive cocci (e.g., coagulase-positive *Staphylococcus*) and the *Enterobacteriaceae* species (especially *Escherichia coli* and *Klebsiella* and *Pseudomonas* species) are prevalent among patients with profound depressions in circulating granulocytes (<500/mm^3). These are particularly common in hospitalized patients. Because of regional differences, certain infectious organisms (e.g., *Acinetobacter* or *Enterobacter*) are prevalent in some hospitals. Coagulase-negative *Staphylococcus* (e.g., *S. epidermidis*) is a well-recognized pathogen in these patients; however, the prevalence of pneumonia caused by these organisms is unknown.

Fungal infections common in immunocompromised hosts include both filamentous fungi (*Aspergillus* species and the *Phycomyces*, such as *Mucor*) and the dimorphic fungi that exist primarily as yeasts in humans. The yeastlike fungi include *Candida*, *Cryptococcus*, *Blastomycoses*, and *Histoplasma* species. Primary host defenses against the filamentous fungi and *Candida* species are phagocytes, such as the granulocyte. Neutropenia and phagocyte dysfunction, therefore, are the major risks for fungal infection. The depth and duration of profound neutropenia predict infection risk by filamentous fungi. Recent data suggest that neutropenia of only a few days' duration is seldom associated with *Aspergillus* infection. Corticosteroid use during exposure to a large number of spores can lead to infection even without neutropenia.

Candida species, especially *C. albicans*, are part of the normal flora within the gastrointestinal tract. Local overgrowth in the mouth (thrush), vagina, esophagus, and gut is frequent in patients with deficient granulocyte number or function. Phagocyte function appears to be the principal defense against these dimorphic fungi. The role of humoral and cell-mediated immunity is unknown. Prophylactic fluconazole administered in the setting of marrow transplantation is associated with a decreased incidence of *C. albicans* infections but with a rise in more antifungal-resistant *Candida* species (e.g., *C. krusei*).

The diagnostic approach to suspected lung infection in an immunocompromised patient requires assessment of the patient's clinical history and infection risk. Infections

can progress rapidly. Fortunately, specific treatments exist for many of the infectious causes of pneumonia. Clinical outcome often depends on prompt recognition of the specific infection and selection of appropriate therapy; consequently, in the presence of pulmonary signs and symptoms, maintain a low threshold for considering infection while awaiting results of further diagnostic tests.

Key factors to consider in evaluating pulmonary disease in the patient with leukemia are the (1) rapidity of onset, (2) severity of illness, (3) radiologic pattern, and (4) presence of extrapulmonary manifestations. These factors will often determine the tempo of the diagnostic evaluation and institution of treatment.

Rapid onset and progression of pulmonary disease should trigger prompt evaluation and institution of therapy, which is often empiric. This pattern of presentation is typical of certain infections and can assist in identifying probable causes. Infections with the most explosive onsets tend to be bacterial, both gram-positive cocci and gram-negative enteroteria. *Legionella* infections can be rapid in onset also, but tend to follow a prodromal period of fever and constitutional symptoms. Pneumonias caused by the herpes viruses, as well as parasitic infections such as *Pneumocystis carinii* pneumonia, can present with little prodrome and progress in a matter of days to respiratory failure.

Gradual or insidious onset is seen more frequently in infections from filamentous fungi, dimorphic fungi, *Nocardia* organisms, mycobacteria, and most opportunistic infections. In addition, a slow onset of symptoms is more common with noninfectious causes of pulmonary disease in the patient with leukemia. Drug-induced lung injury and fibrosis and leukemic infiltration of the lung are rarely explosive in presentation. The exceptions are acute respiratory distress syndrome (ARDS) and pulmonary hemorrhage. As in other patients, ARDS related to sepsis, reaction to incompatible blood products, or other causes can develop rapidly. Likewise, pulmonary hemorrhage can present acutely. Rapid onset of pulmonary hemorrhage is seen more commonly in invasive fungal infection or in ARDS associated with profound thrombocytopenia and bleeding diatheses (e.g., related to uremia or endogenous anticoagulants).

Considerations of the clinical severity of lung disease (primarily symptoms and hypoxemia) are analogous to the rapidity of onset. Although any infection can present with few clinical manifestations, infections that classically present this way include those from locally invasive filamentous fungi, *Nocardia*, and mycobacteria. More severe presentation is typical for bacterial and viral pneumonias, as well as other opportunistic infections.

Characteristics of the chest radiograph are useful in differentiating likely causes of infection in the patient with leukemia having pulmonary manifestations. The most relevant distinction is between diffuse and focal (or multifocal) processes. A diffuse interstitial and alveolar filling process is highly suggestive of either an opportunistic infection or a noninfectious cause of lung injury. Diffuse presentation is not typical of bacterial or filamentous fungal (or *Candida*) pneumonias; however, bacteria or fungus can complicate diffuse lung disease of other causes. *Herpes* group viral and *P. carinii* pneumonias often result in diffuse lung involvement; pleural effusions are uncommon. In addition, pulmonary infection with the dimorphic fungi (e.g., *Histoplasma*, *Coccidioides*, and so on) can also be diffuse. Drug-induced injury, ARDS, cardiac pulmonary edema, and pulmonary leukostasis are the usual noninfectious causes of diffuse involvement.

Important characteristics of focal infiltrates to note are cavitation and organization into masslike lesions, as opposed to alveolar consolidation. The most frequent cause of focal infiltrates is bacterial pneumonia. These infiltrates usually appear as areas of alveolar consolidation. Cavitation suggests a diagnosis of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *E. coli*, anaerobes, or *Rhodococcus equi*. In addition, cavitation is consistent with the necrotic inflammatory nature of *Legionella* infections. Multiple areas of bronchopneumonia with possible cavitation are often seen in herpes simplex virus (HSV) pneumonia secondary to aspiration of infected oral secretions. Mycobacterial infection also largely presents as focal infiltrates (as in the normal host). Masslike lesions, especially with cavitation, are most suggestive of invasive filamentous fungi. These masses can expand without regard to lobar fissures and tissue plains. *Nocardia* infection has a similar presentation and often directly involves extrapulmonary thoracic structures. Pleural effusions present

may be associated with pleural extension of fungal or nocardial disease. Noninfectious causes of pulmonary disease that present as focal infiltrates are most commonly hemorrhage related to a focal infection or focal leukemic infiltrate. Cavitation in these situations is unusual.

Extrapulmonary manifestations can also provide important diagnostic information. Findings such as pleural effusions, cardiomegaly, extrapulmonary soft-tissue masses, and bony lesions may point to specific causes.

The most important components in the evaluation of the cause of possible lung infection in an immunocompromised host are the history and physical examination, supplemented by appropriate laboratory tests. At the very least, it is prudent to obtain complete blood counts, electrolytes, blood urea nitrogen and creatinine, urinalysis, and a chest radiograph.

Microbiological evaluation is crucial. Blood cultures should be obtained routinely as early as possible. Purulent secretions from any site should be cultured for bacteria and fungus on appropriate Gram stain media, and examined after potassium hydroxide (KOH) treatment for fungal elements. This can include needle aspiration or punch-biopsy of suspicious skin lesions. In situations with a high likelihood of fungal disease, methenamine silver staining of clinical material should be included. Unilateral pleural effusions should be sampled by thoracentesis. Bilateral effusions in the clinical setting of congestive heart failure and no fever usually do not warrant examination.

The most valuable purulent material in pulmonary cases is obtained from the tracheobronchial tree. When available, sputum should be cultured for bacteria (as noted above) and for *Legionella* (on charcoal-yeast extract for 1–2 weeks). Rapid detection methods using monoclonal antibody techniques for *L. pneumophila* and *L. micdadei* may be useful. In addition, rapid viral culture and fluorescent antibody staining for respiratory pathogens, especially the *herpes* group, should be performed. Fluorescent antibody staining for respiratory viral pathogens may be available even if a viral laboratory for culture is not. In highly suggestive cases, culture of viral throat and skin lesions may be warranted.

Diagnostic procedures to obtain secretions, washings, or even lung tissue should be performed if (1) expectorated sputum is not available for analysis; (2) the clinical presentation does not strongly suggest a specific cause; or (3) the appropriate clinical response to therapy does not follow promptly. Fiberoptic bronchoscopy (FOB) is the procedure of choice for sampling areas of radiographic abnormality by either telescoping (protected-specimen) brush, bronchoalveolar lavage (BAL), or transbronchial biopsy. Probably little role is found today for transtracheal aspiration to obtain *uncontaminated* lower respiratory tract secretions.

The initial procedure to evaluate immunocompromised hosts with pulmonary disease should be FOB with BAL. Specimens should be evaluated by cell counts, bacterial culture (preferably quantitative), fungal, *Legionella*, mycobacterial cultures, and Gram, methenamine-silver, acid-fast and Wright–Giemsa stains. If available, viral culture and FA staining for cytomegalovirus, HSV, varicella zoster virus, respiratory syncytial virus, adenovirus, and other respiratory viruses should be obtained. FOB also may be the procedure of choice in the evaluation of focal infiltrates or bronchopneumonia. Either protected-specimen brush or BAL can obtain diagnostic material for microscopic or quantitative culture. The diagnostic yield for bacterial infections appears to be high. Although the yield in patients receiving antibiotics may be lower, a pure culture of an organism in this setting is highly suggestive and should prompt appropriate treatment. Filamentous fungi may be recognized in stained material in approximately half of these cases; cultures are positive less often. The yield of opportunistic infections (e.g., *Legionella* and mycobacteria) is unknown, but positive results have been reported. With the possible exceptions of detecting tissue-invasive filamentous fungi or leukemic infiltration, it is not clear that transbronchial biopsy adds significantly to the diagnostic potential of FOB in the typical patient with leukemia.

Percutaneous fine needle aspiration (FNA) is a useful technique for sampling peripheral lesions that may not be approached easily by FOB. The diagnostic yield with FNA is probably highest from masslike lesions and lower from diffuse or infiltrative ones. Depending on operator experience and location of the lesion, the complication rate can be as low as 15% in patients with platelet counts of at least 30000/mm^3.

FNA may be the procedure of choice in lesions in which filamentous fungi is highly suspected.

Sampling of large and multiple areas of lung tissue can be achieved at thoracotomy with an open lung biopsy, which can be performed safely in many patients. Video-assisted thorascopic surgery offers a potentially less morbid approach to biopsy with the same diagnostic yield and expense. Adequate platelet support (counts > 50,000/mm^3) and the absence of bleeding diathesis are important prerequisites.

Two proper places are seen for lung biopsy in the diagnostic evaluation of the immunocompromised patient with pulmonary disease. The first is rapidly progressing and severe pneumonia. In such cases, insufficient time may exist for an empiric trial of therapy (or the empiric therapy may be relatively contraindicated) and specific treatment may be necessary for patient survival. In such cases, lung biopsy may be appropriate to achieve the highest probability of the most specific treatment in the shortest time interval. The second (and more common) place for lung biopsy is with persistent, undiagnosed lung disease, despite attempts at less-invasive diagnostic procedures and empiric therapy.

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XI. NEOPLASTIC DISEASES

102. BRONCHIAL CARCINOIDS AND BENIGN NEOPLASMS OF THE LUNG

David P. Kupferberg

Bronchial carcinoids and *benign neoplasms* of the lung account for less than 10% of all primary pulmonary neoplasms. They represent a clinical challenge because, when centrally located, they are often *roentgenographically silent* and cause slowly progressive airflow obstruction, which can be confused with chronic airways disease.

When peripheral, these tumors are usually *clinically silent* but pose the diagnostic challenge inherent in any solitary pulmonary nodule. Carcinoid tumors are no longer classified along with benign bronchial adenomas, considering they can behave as low-grade carcinomas. Hamartomas are the most common benign pulmonary neoplasms. Leiomyomas, true bronchial adenomas, lipomas, chondromas, fibromas, endometriosis, and teratomas also occur, as well as others.

Bronchial carcinoids comprise the second largest group of lung tumors behind those usually characterized as *bronchogenic carcinoma* and are responsible for approximately 0.5% to 2% of all bronchial tumors. They occur with a small increased frequency in women, with an earlier average age of onset, 40 to 60 years, as compared with non-carcinoid bronchogenic malignancies. Some studies suggest a greater incidence in whites than in African-Americans. Smoking does not play a role in the pathogenesis of these tumors.

Bronchopulmonary carcinoid tumors account for 25% of all carcinoid tumors. Most occur in the gastrointestinal tract. The bronchial type tends to develop centrally, in the large airways, within easy bronchoscopic visualization. Macroscopically, they can grow primarily either as a polypoid lesion or as a predominantly infiltrative process, with only minimal protrusion into the bronchial lumen (known as *iceberg tumor*). Growth is largely submucosal, and the surface epithelium is usually intact, although frequently metaplastic. Carcinoids have a wide histologic spectrum; most commonly, they appear as clumps of small, uniformly staining cells with a richly vascular stroma. Some form acini and produce mucin, however, and others appear highly malignant and may bear a striking resemblance to small-cell carcinoma. Much discussion has involved redefining the histology of these tumors of neuroendocrine origin. They can be classified along a spectrum as follows: (1) typical carcinoid with the best prognosis and bland-appearing histology; (2) atypical carcinoid with one to two mitoses per high power field and necrosis; (3) large-cell neuroendocrine carcinoma with a higher mitotic rate, greater atypia, and necrosis; and (4) small-cell carcinoma, the most aggressive. They appear to be derived from a precursor cell closely related to the Kulchitsky's cell of bronchial mucous glands and reveal neurosecretory granules on electron microscopy. The tumor is capable of elaborating a wide spectrum of neuroendocrine products. Careful interpretation of bronchoscopic biopsies is necessary, considering the similarities between small-cell carcinoma and carcinoid can be exaggerated in the setting of crush artifact and frozen sectioning.

The clinical manifestations of bronchial carcinoid tumors depend on the site of the tumor. Approximately 80% of bronchial carcinoids are central and can produce symptoms and signs of bronchial obstruction, including cough, fever, chest pain, and often a localized wheeze. Hemoptysis is present in approximately 50% of bronchial carcinoids, reflecting both their central origin and their hypervascularity. Peripheral carcinoids most often are asymptomatic and are usually detected fortuitously by roentgenogram. Regional lymph node metastasis is present in approximately 10% of typical carcinoids at presentation, compared with 30% to 50% of atypical carcinoids.

Rarely, an associated is found between paraneoplastic manifestation, the most common of which is Cushing's syndrome, that can even predate visualization of a lung nodule. Acromegaly has also been reported with significantly elevated levels of growth hormone even without overt acromegalic features. The carcinoid syndrome occurs

infrequently with an incidence as low as 0 to 3%. Production of high levels of 5-hydroxytryptamine and other substances (e.g., bradykinin, prostaglandins) enter the systemic circulation, cause the flushing, wheezing, anxiety, vomiting, and hypotension. In addition, cardiac valvular damage can occur on the left side of the heart in bronchial carcinoid syndrome, as opposed to the abdominal variety, in which it occurs on the right side. This syndrome always reflects metastasis of the carcinoid tumor, usually to the liver. Other neuroendocrine manifestations include the Zollinger–Ellison syndrome, hyperinsulinemia, and an association with multiple endocrine neoplasia type-I.

The roentgenographic findings depend on the site of the tumor. In central tumors, bronchial obstruction causes pneumonitis, atelectasis, bronchiectasis, and collapse. The partial collapse can result in hypoxic vasoconstriction and oligemia with expiratory gas trapping. Nonobstructive central and peripheral tumors may appear as a solitary pulmonary nodule, usually 4 cm or less in diameter, and often slightly lobulated. Atypical carcinoids tend to be larger. Calcification can be present. Computed tomographic (CT) scanning is helpful in identifying endobronchial lesions as well as lymph node enlargement. Because carcinoid tumors tend to be highly vascular, there is marked enhancement with intravenous contrast. Newer localization modalities include radiolabeled somatostatin analog scintigraphy (^{123}I-octreotide), which has been reported to find up to 85% of all primary and metastatic carcinoid lesions.

Pulmonary function testing is usually normal unless central obstruction occurs, in which case flow obstruction may be demonstrable. Serum or urine hormone levels can be elevated, which is associated with the aforementioned neuroendocrine syndromes.

The differential diagnosis includes all causes of solitary pulmonary nodules and obstructing airway lesions. The diagnostic evaluation should proceed in a similar fashion as for those lesions. The diagnosis is usually made at bronchoscopy in central tumors but requires other methods (usually thoracotomy) with peripheral tumors.

The frequent hypervascularity of some of these tumors can lead to vigorous bleeding after either bronchoscopic biopsy or transcutaneous needle aspiration. Appropriate precautions should be taken when these procedures are performed.

Treatment for bronchial carcinoids is surgical. Lung-sparing procedures, which have been shown to yield similar survival results, should be attempted when possible. Lymph node dissection should be performed when appropriate. Sleeve resection or lobectomy is often required for the larger and more infiltrative lesions; lobectomy is often necessitated by bronchiectasis and parenchymal necrosis, distal to an obstructive tumor. In such cases, the prognosis is excellent. A role may be seen for Nd:YAG laser resection in typical carcinoid, particularly when patients are not good surgical candidates. Local recurrence rates are slightly higher. Survival rate in cases of nonmetastatic typical carcinoid is approximately 90%. Atypical carcinoid has a 5- and 10-year survival of 60% and 40%, respectively. Positive lymph nodes and larger tumor size correlate with a poorer overall prognosis. Chemotherapy has limited benefit for metastatic disease when patients are unresponsive to other treatments, and overall, it has limited use. Metastatic liver lesions have been treated successfully with hepatic artery embolization and local direct chemotherapeutic instillation. Interferon and octreotide have been reported to temporarily stabilize tumor growth, yet rarely produce any decrease in tumor size. Cushing's syndrome can be well controlled with octreotide with significant improvement in symptoms.

Pulmonary hamartomas, which are the largest group of benign pulmonary neoplasms, occur more frequently in men than in women (3:1), with a peak incidence in the seventh decade. They are uncommon before the age of 30. Pathologically, they contain a mixture of tissues normally present in lung (i.e., smooth muscle, collagen, and rarely, cartilage); however, these components are totally disorganized. Ultrastructural studies indicate that pulmonary hamartomas represent a histologic spectrum of mesenchymal neoplasms derived from peribronchial connective tissue. Although pulmonary hamartomas can become extremely large, they remain benign.

Hamartomas are clinically silent because of their peripheral location. Hemoptysis is rare. Roentgenographically, they appear as well-circumscribed, solitary pulmonary nodules, usually less than 4 cm in diameter; occasionally, they can be large, nearly filling the hemithorax. Calcification, resembling a kernel of *popped* popcorn, occurs in 5% to 15% of cases. CT scan of the lung may suggest the diagnosis. Multiple tumors rarely

occur. Unless the roentgenogram and clinical course are classic, the diagnosis is made at thoracotomy because other methods usually fail to exclude carcinoma.

Infrequently, primary lung involvement by other benign neoplasms is seen. Depending on the site of involvement, central versus peripheral, symptoms or signs are seen of bronchial involvement (e.g., cough, hemoptysis, recurrent pneumonia) or no clinical findings are evident. Roentgenographically, findings may be consistent with bronchial obstruction or only solitary or multiple nodules. True bronchial adenomas are benign tumors that arise from bronchial mucous glands and are quite rare. They can cause symptoms by obstructing airways. Leiomyomas arise from smooth muscle of the lung and are usually endobronchial. Most cases are asymptomatic. Women are affected more often than men, and the average age at presentation is 37. There appears to be a distinct entity in which multiple pulmonary fibroleiomyomas occur in women who have had uterine fibroids. Although such tumors are histologically and clinically benign, controversy exists regarding their *in situ* or *metastatic* origin. Lipomas are usually endobronchial (80%) and can occur on either side of the bronchial cartilage. They can change shape roentgenographically, as the individual assumes different positions. Chondromas are extremely rare. Unlike hamartomas, they derive exclusively from formed bronchial cartilage. Teratoma is a relatively common tumor of the mediastinum but rarely is it found in the lung. Pulmonary teratomas may contain tissue from any germ layer. Roentgenographically, they may contain calcifications or even well-formed teeth. Expectoration of hair (trichoptysis) has been reported. Endometriosis can occur in the lung as a solitary nodule. The origin of this tumor in lung is unclear; some consider it of metastatic origin, whereas others feel it arises from pleuripotential pulmonary tissue. Recurrent pneumothorax, particularly on the right side, or hemoptysis associated with menstruation should suggest the diagnosis.

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103. LUNG CANCER: CLASSIFICATION, PATHOLOGY, AND EPIDEMIOLOGY

John E. Barkley

The incidence of lung cancer continues to increase worldwide. According to American Cancer Society estimates, 172,000 new cases and 160,000 deaths will have occurred from lung cancer in the United States in 1999. Recent data suggest that male death

rates from lung cancer may have plateaued; however, the estimated 91,000 male deaths still exceeds the combined rate of deaths from prostate, colon, and pancreatic cancer. The incidence of lung cancer among women continues to increase and now accounts for 25% of all female cancer deaths. In contrast, breast cancer accounts for 16% of female cancer death. Over the past 20 years, the male preponderance of 5 to 7:1 has fallen to its current level of 1.2:1 because of the striking increase in lung cancer among women. Presumably, this changing pattern of disease is caused by the post-World War II increases in cigarette smoking in the general population and in women in particular.

The term *lung cancer* is composed of a number of specific malignancies (Table 103.1). Most classifications, including the one by the World Health Organization, divide lung cancer into four major types: squamous or epidermoid, adenocarcinoma, large-cell carcinoma, and small-cell carcinoma (SCLC). With the exception of the small-cell type, these classifications are poorly predictive of tumor behavior. As a result, the clinician has been concerned primarily with the division of lung cancer into SCLC and non-SCLC types.

For reasons that remain undefined, the incidence of squamous cell carcinoma has declined in the United States. At the same time, an increase has occurred in the incidence of adenocarcinoma, which is now the most common histologic subtype, accounting for 30% to 50% of primary lung cancers. In some series, bronchioalveolar carcinoma is responsible for much of the increasing incidence of adenocarcinomas.

Squamous cell carcinoma arises from altered bronchial epithelium and is preceded by years of progressive mucosal changes that include squamous metaplasia, dysplasia, and carcinoma *in situ*. In its early stages of growth, the tumor can appear as a small, red, granular plaque or as a focus of leukoplakia. Later, it can appear as a large intrabronchial gray–white or yellow mass. Cavitation can occur in the lung distal to the obstructing mass. Microscopically are seen intercellular bridges connecting the abnormal neoplastic cells and abundant keratin formation. The latter can be considerably reduced or absent in the poorly differentiated subtypes. Characteristically, superior sulcus tumors (Pancoast's tumors), if squamous in cell type (50%), are well differentiated.

Adenocarcinomas are classically peripheral tumors arising from the peripheral airways and alveoli; however, these tumors also can arise proximally from the epithelium or submucosal glands. When bronchial in origin, they are almost impossible to distinguish on a cytologic basis from metastatic pancreatic, renal, breast, and colonic adenocarcinoma. When peripheral, they can be similarly difficult to distinguish from metastatic adenocarcinoma or malignant mesothelioma. Peripheral adenocarcinomas are usually

Table 103.1. Histologic classification of malignant lung tumors

Squamous cell carcinoma (epidermoid carcinoma) variant
–Spindle (squamous) carcinoma
Small-cell carcinoma
–Oat-cell type
–Intermediate cell type
–Combined oat-cell carcinoma
Adenocarcinoma
–Acinar adenocarcinoma
–Papillary adenocarcinoma
–Bronchoalveolar carcinoma
–Solid carcinoma with mucous formation
Large-cell carcinoma variants
–Giant-cell carcinoma
–Clear-cell carcinoma
Adenosquamous carcinoma
–Carcinoid tumor
–Bronchial gland carcinoma
Adenoid cystic carcinoma
–Mucoepidermoid carcinoma
–Others

well-circumscribed, gray–white masses that rarely cavitate. Microscopically, a spectrum is seen of well-developed to poorly developed cuboidal or columnar cells having microvilli and forming glandlike structures that may or may not produce mucin. In the bronchioalveolar type, 40% to 50% of which secrete mucin, the cylindrical tumor cells grow along the wall of the alveoli.

Small-cell carcinoma begins as a submucosal disease and usually develops proximally as a large, bulky, soft, gray–white mass. When bronchial narrowing occurs, it commonly results from circumferential encasement by extraluminal tumor. Microscopically, small-cell carcinomas are composed of fusiform, round, or polygonal cells approximately twice the size of lymphocytes, with inconspicuous nucleoli and modest amounts of cytoplasm. The presence of cytoplasmic dense-core granules has led to the concept that SCLC belongs in a group of tumors derived from neuroendocrine cells that are responsible for the production and secretion of specific peptide products. Although SCLC is divided into oat-cell, intermediate cell, and combined cell patterns, it is unclear whether these subtypes differ in their natural history or response to therapy.

Large-cell carcinomas, as with adenocarcinomas, are usually located peripherally. They can be quite large and not infrequently cavitate. Microscopically, they have large nuclei, prominent nucleoli, abundant cytoplasm, and distinct cytoplasmic membranes. Large-cell carcinomas lack evidence of either squamous or glandular differentiation; many represent undifferentiated forms of adenocarcinoma or squamous cell carcinoma.

Abundant epidemiologic data, as well as experimental animal data, point to the accoutrements of modern industrialized society as producing the major risks for lung cancer. Tobacco smoking appears to be the greatest risk (and causal) factor, with the relative degree of risk dependent on the number of cigarettes smoked per day, the duration of smoking in years, the depth of inhalation, the tar and nicotine content in the cigarettes smoked, and incompletely defined genetic factors. Prospective and retrospective studies have demonstrated an increased (8–20 times) death rate from lung cancer in smokers versus nonsmokers. Heavy smokers (more than 25 cigarettes/day) experience a risk that is 20 times that of nonsmokers. Carcinogenic risk in former smokers declines progressively for 15 years following smoking cessation, after which the risk approaches that of lifelong nonsmokers. The residual risk experienced by the former smoker is determined by his or her prior smoking history. In the group with the heaviest smoking history, the residual risk probably never returns to that of a lifelong nonsmoker.

Although the exact risk of passive smoking (secondhand smoke) remains controversial, current data suggest no zero-risk threshold for exposure and that a dose-response relationship exists between extent of exposure and risk. Estimates have ranged from 500 to 5000 lung cancer-related deaths per year from passive smoking in the United States.

More than 2000 chemicals are found in cigarette smoke; several of them are either direct carcinogens or cocarcinogens in animal (particularly hamster) models. In humans, smoking induces a spectrum of histologic changes in the bronchial epithelium that are not seen in nonsmokers. These changes include loss of bronchial cilia, basal epithelial hyperplasia, and nuclear abnormalities. The severity of such changes increases in heavy smokers and tends to be most severe in patients dying from lung cancer. Smoking-induced alterations in bronchial mucosa can slowly resolve in individuals who stop smoking.

Certain occupational factors can substantially increase the risk of lung cancer. An increased risk has been reported among workers in several industries, including metallurgy, mining, and manufacturing of industrial gases, pharmaceutical preparations, soaps and detergents, paints, inorganic pigments, and synthetic rubber. Specific pulmonary carcinogens include arsenic, asbestos, chloromethyl methyl ether, bischloromethyl ether, chromium, ionizing radiation, mustard gas, nickel, radon, and vinyl chloride. Many are additive or synergistic with cigarette smoke in the induction of pulmonary malignancies. Nonsmoking asbestos workers have a fivefold increased risk of death from lung cancer, as compared with other nonsmoking workers. Asbestos workers who smoke one pack of cigarettes per day experience a 90 times increased risk, as compared with unexposed nonsmokers.

The role of air pollution in carcinogenesis is uncertain. The incidence of lung cancer in urban residents is only 1.2 to 2.3 times that of rural residents. The reducing types of pollutants (e.g., sulfur dioxide, carbonaceous particulate matter) are thought to be

the major carcinogens, whereas oxidants (e.g., hydrocarbons, nitrous oxides) are not considered important. Individuals with heavy exposure to motor vehicle emissions do not appear to have an increased incidence of lung cancer.

Significant individual susceptibility to lung cancer may exist. Some studies suggest a familial predisposition; the incidence of lung cancer in close relatives of patients with this neoplasm appears to be two to three times that of the general population. Also seen is an association of lung cancer with certain diseases. Lung cancer can complicate pulmonary parenchymal diseases such as diffuse pulmonary fibrosis, sarcoidosis, and scleroderma. As many as 10% of patients with pulmonary fibrosis will die from bronchogenic carcinoma. Emphysema and chronic bronchitis with airflow obstruction also represent independent risk factors for the development of lung cancer, even when age, gender, and smoking history have been controlled for.

Finally, certain dietary factors can modify the risk of lung cancer. Retrospective epidemiologic studies have demonstrated an inverse relationship between the risk of lung cancer and the intake of fruits and vegetables that contain beta-carotene. High consumption of beta-carotene, which is subsequently converted to retinol, has been associated with an approximate 50% reduction in the risk of lung cancer in comparison with low consumption. However, three prospective, randomized, controlled intervention trials found no benefit or increased incidence of death from bronchogenic carcinoma in those patients given beta-carotene as a dietary supplement.

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104. LUNG CANCER: CLINICAL PRESENTATION, DIAGNOSIS, STAGING, AND PROGNOSIS

John E. Barkley

Patients with *bronchogenic carcinoma* present in a variety of ways including (1) asymptomatic; (2) symptoms of local disease; (3) symptoms of metastatic disease; and (4) symptoms of paraneoplastic syndrome. The histologic type of lung cancer (non–small-cell vs. small cell), site of origin (central vs. peripheral airways), the inherent biologic activity of the neoplasm, and comorbid conditions all determine how an individual patient will present.

Only 25% to 40% of patients present with early stage disease that is potentially resectable. Of these, perhaps 20% present with an incidental abnormality discovered on a chest radiograph. The remainder with early stage disease present with signs and symptoms of local tumor growth, including cough, dyspnea, wheezing, or hemoptysis. Additionally, patients can present with purulent sputum, fever, and chills from postobstructive pneumonia. More ominous signs and symptoms of local tumor growth include superior vena cava syndrome, Horner's syndrome, dysphagia, odynophagia, hoarseness, elevated hemidiaphragm from phrenic nerve impingement, dyspnea and chest pain from pleural effusion, and dyspnea and hemodynamic compromise from pericardial involvement.

Patients with *metastatic disease* usually have general symptoms of malaise and anorexia with or without weight loss. Other symptoms depend on the site(s) of metastases. The most common sites are supraclavicular and cervical lymph nodes, brain,

bone, liver, and adrenal glands. However, no organ system is exempt from possible metastatic deposits.

Some patients present with signs or symptoms of a paraneoplastic syndrome. They can be divided into five categories: (1) endocrine-metabolic; (2) neuromuscular; (3) hematogic-vascular; (4) dermatologic; and (5) skeletal and connective tissue (see Chapter 106).

Clinical staging of lung cancer requires logical use of currently available diagnostic techniques. The approach should be to confirm that an intrathoracic lesion is a cancer, define its cell type, and accurately determine the extent of disease by the least invasive means available.

The first step in this diagnostic approach is to define the nature of the intrathoracic lesion as either malignant or benign. The relative difficulty of this first step differs for central (endobronchial) and peripheral lesions. For endoscopically visible central lesions, a positive tissue diagnosis can be made in essentially all cases by means of sputum and fiberoptic bronchoscopy. For peripheral lesions, the bronchoscopic yield is dependent on the size of the lesion (the lowest yield occurring with lesions <2 cm) and its location. Overall yield for peripheral lesions is increased with a combination of washings, brushings, transbronchial biopsies, and a transbronchial needle aspiration (TBNA). Transthoracic needle aspiration of peripheral lesions, especially when performed under computed tomography (CT) guidance, can substantially increase the yield. A negative bronchoscopic examination and needle aspiration, however, cannot absolutely exclude the possibility of cancer. Unless a specific diagnosis is obtained, a thoracotomy or a period of careful observation in higher-risk surgical patients is indicated.

For non–small-cell lung cancer (non-SCLC), the International System for Staging Lung Cancer is used (Table 104.1). Several classification changes were made in the most recent revision in 1997: (1) noninvasive tumors (Tis) are stage 0; (2) T3 tumors invade structures but can be resected; (3) T4 tumors now include those primary tumors with satellite lesions in the same lobe; (4) satellite nodules in the ipsilateral lung but different lobe represent M1 disease; (5) stage I and II are now IA/IB and IIA/IIB, based on the size of the primary tumor and presence or absence of N1 nodes; and (6) T3N0M0 lesions are now classified as stage IIB.

To define the T characteristics of a lesion, chest x-ray study, CT scanning, positron emission tomography (PET), magnetic resonance imaging (MRI), and bronchoscopy can all be helpful. MRI can be particularly useful in assessing patients with possible T3 or T4 lesions.

To accurately define the N (nodal) status of a lesion, some combination of chest radiography, CT scan, PET, TBNA, ultrasound-guided transesophageal needle aspiration, mediastinoscopy, mediastinotomy, and thoracotomy is required.

Generally, most now agree that nodal enlargement identified by CT requires tissue confirmation of metastasis by mediastinoscopy or alternate biopsy technique, except when gross mediastinal invasion by tumor (T4) is present. A patient should not be denied potentially curative surgery based solely on radiographic criteria. Emphasizing this point, a recent study demonstrated that 36% of lymph nodes measuring 2 to 4 cm in short-axis diameter on CT did not contain metastases at the time of surgery. CT scanning is also useful in identifying the site(s) of mediastinal node enlargement, especially those that may not be accessible to standard mediastinoscopy, such as aortopulmonary nodes (American Joint Committee on Cancer [AJCC] station 5); anterior mediastinal nodes (AJCC station 6); paraesophageal nodes (AJCC station 8); and inferior pulmonary ligament nodes (AJCC station 9). Also, extending the CT examination to include the adrenal glands and liver often detects the presence of occult metastatic disease. Considerably less agreement is found on the need for mediastinoscopy in patients with normal lymph nodes seen on CT. Some authors suggest that patients with T1 tumors and mediastinal nodes with a short-axis diameter of 10 mm or less can proceed directly to thoracotomy without first undergoing mediastinoscopy. Others disagree, citing a significant incidence of intranodal tumor in normal-sized lymph nodes. The role of MRI scanning remains limited because of its poorer spatial resolution compared with CT, its expense, and its limited ability to detect calcification.

Previously, radiographic imaging has been limited to anatomic considerations only. The advent of PET allows assessment of the metabolic activity of lesions, with malignant lesions tending to be hypermetabolic. Several recent studies have demonstrated

Table 104.1. Staging of non–small-cell lung cancer—TNM definitions

PRIMARY TUMOR (T)
TX: Occult carcinoma.
T0: No evidence of primary tumor.
Tis: Carcinoma *in situ*.
T1: Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, and without bronchoscopic evidence of invasion proximal to a lobar bronchus. (i.e., not main bronchus).
T2: A tumor >3 cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis that extends to the hilar region; at bronchoscopy, proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2 cm distal to the main carina; any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.
T3: A tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral bodies; or a tumor in the main bronchus within 2 cm of main carina without involving it.
T4: A tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral bodies, or main carina; or with the presence of malignant pleural effusion, satellite nodule in the same lobe.

NODAL INVOLVEMENT (N)
NX: Occult carcinoma.
N0: No regional lymph node metastasis.
N1: Metastasis of lymph nodes in peribronchial or ipsilateral hilar region, or both, including direct extension.
N2: Metastatic involvement of ipsilateral mediastinal lymph nodes, subcarinal lymph nodes, or both.
N3: Metastatic involvement of contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, or ipsilateral or contralateral scalene or supraclavicular lymph nodes.

DISTANT METASTATIC INVOLVEMENT (M)
M0: No (known) distant metastatic involvement.
M1: Distant metastatic disease involvement (specify site(s)); tumor nodule(s) in the ipsilateral lung nonprimary tumor-bearing lobe

T, tumor; N, node; M, metastasis.

the superiority of PET over CT scanning in the staging of bronchogenic carcinoma. Optimal results are achieved by combining CT and PET images. The major current limitation of PET is its lack of widespread availability.

Several series have demonstrated the ability of TBNA to sample mediastinal nodes. False-positive aspirates, although rare, have been reported, and contamination should be suspected if TBNA contains a number of columnar epithelial cells and a paucity of lymphocytes and malignant cells, or if the aspirate is performed adjacent to a parenchymal mass that abuts the mediastinum. Whether a positive aspirate from an enlarged mediastinal node has the same prognostic and therapeutic implications as a positive aspirate from a normal-sized lymph node is unknown.

To define the M (metastasis) characteristics of a lesion, a thorough history and physical examination, chemistry panel, liver function tests, chest x-ray study and CT scan of the chest (to include the liver and adrenal glands) are recommended. Other diagnostic workup should be guided by the initial evaluation. Specifically, routine bone scanning and cranial CT scanning is not recommended. It should be pointed out that some authorities recommend cranial CT scanning in patients with known adenocarcinoma because of the 5% to 10% risk of asymptomatic metastatic disease. Finally, initial experience

with whole body PET indicates that unsuspected metastatic disease can be found in 11% to 29% of patients. This is independent of the central nervous system which is not well imaged with PET. The role of PET in the routine evaluation of patients with bronchogenic carcinoma has yet to be defined.

Stages of lung cancer are defined by combining the tumor-node-metastasis (TNM) components (Table 104.2). Stage I includes those patients with no lymph node involvement (N0) and no invasion of structures. Stage II includes patients with hilar (N1) lymph node metastases and those patients with chest wall invasion and no lymph node involvement (T3N0, stage IIB). Stage III is divided into those with potentially resectable disease (IIIA) and those with unresectable disease (IIIB). Stage IV disease is confined to those patients with metastasis to distant sites.

With advances in understanding the biology of lung cancer and more effective therapeutic interventions, the staging system will continue to be refined. Critical to these advances is accurately staging cancer in patients using the current system. Perhaps the most important part of accurate classification is determination of the N (nodal) status. Routine use of the new AJCC regional lymph node map will allow for uniformity in reporting patient data.

Prognosis is most strongly correlated with stage of disease at presentation. With surgery, the 5-year survival for stage IA, IB, and IIA/IIB disease is approximately 70% to 80%, 50% to 60%, and 35% to 50%, respectively. Stage III patients have a 5-year survival ranging from less than 5% to 25% to 30%, depending on the particular TNM status and treatment modalities used (see Chapter 105). Patients with stage IV disease have a 1-year survival of 10% to 20% and 5-year survival of less than 5%. Occasionally, patients with stage IV disease who respond well to chemotherapy survive 2 to 3 years and longer.

In addition to stage at presentation, the patient's performance status at diagnosis is extremely important prognostically. Finally, several histopathologic markers and molecular biologic characteristics have been found to correlate with survival and may ultimately become incorporated into the staging system.

Small-cell lung cancer is divided into limited and extensive stage disease. *Limited stage* is defined as disease limited to one hemithorax, with or without ipsilateral supraclavicular lymph node involvement. *Extensive stage* disease is everything else. Without

Table 104.2. New International Revised Stage Grouping

Stage	TNM subset
0	Carcinoma *in situ*
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0
	T3N0M0
IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	Any T Any N M1

T, tumor; N, node; M, metastasis.

treatment, survival is 6 to 12 weeks in extensive stage disease and 3 to 6 months in patients with limited stage disease. With modern treatment, median survival is approximately 9 months and 20 months in extensive and limited stage patients, respectively. Five-year survival is less than 5% and 10% to 20%, respectively.

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105. LUNG CANCER: TREATMENT

John E. Barkley

The prognosis for patients diagnosed with lung cancer remains poor. However, this disease remains a major focus of research, and some exciting advances offer significant hope. Specific treatment recommendations are guided by (1) the histologic type of tumor (small-cell vs. non–small-cell); (2) the stage of disease; and (3) a patient's performance status. Optimal evaluation and management require a multidisciplinary team approach, including pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, radiology, pathology, and nursing. Such an approach benefits by an overlapping yet unique input from each specialty area.

The initial goal in managing patients with *non–small-cell lung cancer* (non-SCLC) is to determine whether a patient is (a) operable—the patient will survive surgery with an acceptable risk for morbidity and mortality and (b) the cancer is resectable—the lesion is technically removable and will result in an improved prognosis.

A patient's *operability* is usually assessed by routine cardiovascular evaluation, simple spirometry, and arterial blood gases. In a patient with marginal pulmonary reserve, quantitative ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning and exercise testing can provide additional useful information. $\dot{V}/\dot{Q}$ scanning can be helpful in predicting postoperative pulmonary function. Patients with a marginal FEV_1 may not lose lung function if the lobar bronchus (and artery) to be resected is already obstructed and not participating in gas exchange (or perfusion). Cardiopulmonary exercise testing allows the determination of a patient's maximal oxygen consumption ($\dot{V}o_2max$). The $\dot{V}o_2max$ can be used for further risk stratification. Patients with a $\dot{V}o_2max$ less than 10 ml O_2/kg/min should not be operated on, whereas those with 15 ml O_2/kg/min or greater should do well. Unfortunately, no single test can accurately predict postoperative functional outcome and each patient must be considered individually. Patients with marginal lung function may benefit from preoperative pulmonary rehabilitation as well.

The *resectability* of cancer in an individual patient is determined by the clinical stage of the disease. Both stage I and II disease are resectable by definition and should be treated with surgery whenever possible. Despite the recent refinements in lung cancer

staging, stage III is composed of a heterogeneous group of patients with widely varying 5-year survivals following surgical resection alone. Patients with bulky, multistation N2 disease do poorly with surgery alone and should not undergo primary surgical resection; however, patients with a negative mediastinoscopic examination and single station, microscopic mediastinal modal metastatic disease discovered at thoracotomy may have a 25% to 30% 5-year survival with surgery alone. Patients with stage IIIB (N3 or T4) or stage IV disease usually should not undergo resection, but in rare circumstances are candidates for surgical therapy with curative intent.

Chemotherapy and radiotherapy for non-SCLC can be used preoperatively (neoadjuvant therapy) postoperatively (adjuvant therapy), and separately (sequential) or together (concurrent) as definitive therapy.

Neoadjuvant therapy is an area of active investigation in stage I, II, and III disease. Several phase II and two small phase III studies of neoadjuvant therapy in patients with stage III (N2) disease have been encouraging. However, toxicity can be significant and neoadjuvant therapy outside of the protocol setting cannot currently be recommended.

Adjuvant therapy in patients with completely resected stages I, II, and III disease has been studied. Adjuvant chemotherapy does prolong disease-free survival but not overall survival and should also be considered investigational. Adjuvant radiotherapy, which has recently been reviewed, may be detrimental in patients with early stage non-SCLC (stage I and II). Adjuvant radiotherapy in resected stage III disease decreases the local recurrence rate and may improve long-term survival.

For most patients with stage IIIA (N2) and IIIB disease, a combined or multimodality approach should be considered. With radiotherapy alone, the 5-year survival is less than 10%. By adding induction chemotherapy, (followed by radiotherapy), the long-term survival increases to 17%. Patients with minimal weight loss and good performance status should be considered for combined modality therapy.

Stage IV non-SCLC is almost always incurable but patients may benefit significantly from systemic chemotherapy. Several studies have documented 40% to 60% 1-year survival rates in patients with stage IV disease and good performance status. Several novel chemotherapeutic agents are now available and offer the possibility of improved survival rates with less toxicity.

Without treatment, *small cell carcinoma* is a rapidly fatal disease. Patients with limited stage disease have an average survival of approximately 20 months when treated with concurrent chemotherapy and radiotherapy. The 2-year survival approaches 45% with a 5-year survival of 15% to 20%. Patients achieving complete remission should be considered for prophylactic cranial irradiation (PCI). A common site of relapse in patients achieving remission is metastases to the central nervous system (CNS). The risk of this devastating complication can be reduced from 30% to 10% with PCI. A recent meta-analysis examining PCI reported a survival advantage as well. Late CNS toxicity has been reported and is often cited as a reason not to use PCI. Extensive stage SCLC is fatal in 1 to 3 months without treatment. With combination chemotherapy, average survival increases to 9 to 12 months. Radiotherapy for extensive stage disease is generally reserved for palliation of symptomatic metastatic disease not responding to chemotherapy or at the time of relapse.

The role of surgery in small-cell lung cancer remains controversial. Typically, patients are found to have SCLC during thoracotomy for a solitary pulmonary nodule. Survival in this setting approaches 50%. Although no randomized trials have been performed, the general consensus is to treat these rare patients with adjuvant chemotherapy.

The palliation of patients with unresectable, inoperable, or recurrent disease can involve multiple modalities. As mentioned, more active systemic chemotherapeutic agents are being developed and offer a real opportunity for improving survival without significant toxicity. Radiation therapy is effective at palliating metastatic disease that produces symptoms of pain, cough, hemoptysis, superior vena cava obstruction, and atelectasis. CNS disease can often be palliated with radiation as well. Central airway obstruction in lung cancer is common and can be devastating. Both flexible and rigid bronchoscopy can be invaluable in assisting these patients. Endobronchial stenting, laser therapy, endobronchial radiation therapy (brachytherapy), electrocautery, cryotherapy, balloon dilatation, and photodynamic therapy can all be useful in restoring patency of the central airways and improving the patient's quality of life.

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106. EXTRATHORACIC AND ENDOCRINE MANIFESTATIONS OF LUNG CANCER

Shari A. Brazinsky and Deborah Shure

The extrathoracic manifestations of bronchogenic carcinoma can be divided into those related to local spread, those related to metastases, and those that occur independent of cancer spread—the paraneoplastic syndromes.

Local spread, which causes extrathoracic manifestations, is most often caused by a superior sulcus tumor, which can involve the eighth cervical and first thoracic nerves, causing pain in the shoulder and along the ulnar distribution of the arm. Paravertebral involvement of the sympathetic chain can cause a Horner's syndrome. Tumor can also spread to involve the recurrent laryngeal nerve, causing hoarseness. Superior vena cava syndrome is caused by tumor compression of this vessel anywhere along its course. Other extrathoracic symptoms can be caused by spread into the mediastinum, with involvement of the heart and esophagus.

Although metastatic disease is common in patients dying of lung cancer (96%), symptomatic disease is less frequent. Metastases are most common with lymph nodes (70%), liver (39%), brain (30%), adrenals (25%), bone (20%), and kidneys (18%), although they can involve any organ or tissue in the body. Lymph node, adrenal, and renal metastases

are rarely symptomatic. Bony metastases can produce local pain and even spinal cord compression, if the vertebral bodies are involved. Cord compression must be urgently diagnosed and treated. Liver involvement is generally asymptomatic but can cause abdominal discomfort. Brain involvement can mimic cerebrovascular disease or primary intracranial neoplasm.

The *paraneoplastic syndromes* can be characterized as (1) constitutional, (2) hematologic, (3) skeletal, (4) neuromuscular, (5) cutaneous, (6) vasculitic, and (7) endocrine. Constitutional symptoms such as weight loss, anorexia, and fatigue are probably the most common. Their presence or magnitude cannot be explained by tumor size, and their cause is unknown. Cachexia is a significant prognostic factor in the course of lung cancer. Recent studies suggest that splenic cytokines such as tumor necrosis factor can influence cachexia, as well as tumor growth. Megestrol acetate, a synthetic progestin, has been found to improve well-being, as well as allow weight gain, in many types of lung cancer.

A *normochromic, normocytic anemia* occurs in less than 10% of patients with bronchogenic carcinoma and is unrelated to marrow infiltration or therapy. A number of coagulopathies are associated with lung cancer. They include migratory thrombophlebitis (Trousseau's syndrome), disseminated intravascular coagulation, chronic hemorrhagic diathesis, nonbacterial thrombotic endocarditis, and arterial embolization. Trousseau's syndrome often involves unusual sites such as the upper extremities or the vena cava and is frequently unresponsive to anticoagulant therapy.

Hypertrophic pulmonary osteoarthropathy occurs in 4% to 12% of patients with lung cancer, most commonly with epidermoid carcinoma and only rarely with small-cell carcinoma (5%). It consists of periosteal new bone formation in the long bones, with digital clubbing and symmetric arthritis. Vasomotor instability is often present with episodic blanching, swelling, and diaphoresis of the hands and feet. The ankles, wrists, and long bones can be very painful and tender. Although new bone growth is present, the syndrome does not seem to be caused by ectopic human growth hormone production, but it may be mediated by autonomic reflexes. It usually regresses after tumor removal, vagotomy, or thoracotomy without tumor resection. Prognosis does not appear to be altered if this syndrome is present, and tumor recurrence is frequently accompanied by recurrent osteopulmonary arthropathy.

An increasing number of neuromuscular syndromes have been reported in association with bronchogenic carcinoma, most commonly small-cell carcinoma. These syndromes may precede the clinical appearance of the tumor by months to years. The most potentially devastating are cerebral encephalopathy and cortical cerebellar degeneration, both of which can occur precipitously. Peripheral neuropathies, usually sensorimotor and often presenting as pain and paraesthesias of the lower extremities, occur in up to 15% of patients with lung cancer. This can be followed by the gradual onset of a neuropathic arthropathy. A myasthenia (Eaton–Lambert) syndrome occurs in 6% of patients with small-cell carcinoma and differs from myasthenia gravis primarily by an increase in the muscle action potential on repetitive stimulation and the lack of improvement in muscle strength with anticholinesterases. A symmetric proximal muscle neuromyopathy, which is also common, is associated with muscle wasting. Non–small-cell tumors have been reported with a paraneoplastic necrotizing myopathy. Paraneoplastic encephalomyelitis, frequently associated with small-cell carcinoma, is characterized by inflammatory infiltrates and neuronal loss. A rapidly progressive binocular vision loss, termed *cancer-associated retinopathy*, has been described in patients with small-cell carcinoma.

The cause of these neuromuscular paraneoplastic syndromes is generally not known. Evidence has been found, however, for an autoimmune basis for several of these syndromes. In these cases, antibodies have been found that cross-react with tumor and normal tissue antigens. In Eaton–Lambert syndrome, the antibodies cross-react with presynaptic voltage-gated calcium channels at the neuromuscular junction. In cancer-associated retinopathy, antibodies to a tumor antigen cross-react with a subset of retinal ganglion cells (to the photoreceptor protein recoverin). Prednisone therapy has been reported to reduce antibody titers and stabilize visual fields. A heterogeneous group of cases including of paraneoplastic encephalomyelitis, cerebellar degeneration, Eaton–Lambert myasthenic syndrome, and sensory neuronopathy with small-cell car-

cinoma associated with a specific antibody in the serum or cerebral spinal fluid, is considered part of the anti-Hu syndrome (bearing the name of the first patient in whom the antibody was discovered). These include the presence of high titers of Hu antibody associated with more severe cerebellar degeneration than in the subset without the antibody. An anti-Purkinje cell antibody has also been found in some patients with paraneoplastic cerebellar degeneration. In patients with lung cancer, however, the antibody is rarely found, and the clinical picture is less severe and slower to develop than when the syndrome is associated with other types of cancer. Lower motor neuron disease as a paraneoplastic syndrome has also been seen with anti-Hu antibody. Some studies have found more than one antibody present in patients with paraneoplastic syndrome, raising the possibility of multimodal autoantibody production. Such autoantibodies may be found to be associated with other paraneoplastic syndromes in the future.

Cutaneous manifestations include features of dermatomyositis, hyperpigmentation caused by ectopic production of melanocyte-stimulating hormone, and acanthosis nigricans. The last is a hyperkeratotic, hyperpigmented dermatosis with small papillomatous lesions giving the skin a velvety texture. It is symmetric and prominent in skin folds. When it occurs after age 40, it is almost always associated with cancer (90% intra-abdominal, 5% lung). Dermatomyositis has been found to be associated with an autoantibody to a nuclear complex of unknown function. Other rare manifestations include erythema gyratum (thickened, bandlike urticarial plaques imparting a *knotty pine* appearance) associated with small-cell carcinoma, universal hypertrichosis lanuginosa associated with epidermoid carcinoma, and rapidly progressive digital necrosis associated with small-cell carcinoma. Recently, benign dermatosis granuloma annulare, interstitial granulomatous dermatitis, tripe palms, and subacute cutaneous lupus erythematosus were reported as being temporally associated with carcinoma of the lung, and regressed with successful treatment of the malignancy.

Non–small-cell carcinomas have been associated with cutaneous vasculitis and purpura rheumatica. Disseminated vasculitis has now been reported with small-cell carcinoma of the lung. A nonsystemic subacute vasculitic neuropathy called *paraneoplastic vasculitic neuropathy* has recently been described with small-cell carcinoma of the lung. The neuropathy, which varies from a mononeuropathy multiplex to a symmetric polyneuropathy, is associated with an elevated erythrocyte sedimentation rate and high cerebral spinal fluid protein count. Both chemotherapy and immunotherapy for vasculitis is effective in this disorder.

Many endocrine and metabolic syndromes are associated with bronchogenic carcinoma; they are primarily, but not exclusively, associated with small-cell carcinoma. It is theorized that lung cells embryologically derived from neural crest cells with the ability for amine precursor uptake and decarboxylation undergo malignant derepression and secrete one or more peptide hormones. Overt clinical syndromes appear in approximately 10% of patients with lung cancer, although subclinical hormone production is more common. The hormones produced are peptides and include adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone, parathyroid hormone, antidiuretic hormone (ADH), human chorionic gonadotropin, prolactin, serotonin, insulin, glucagon, corticotropin-releasing factor, and calcitonin. Most is known about ectopic ACTH, parathyroid hormone, and ADH.

Probably the most commonly produced ectopic hormone is ACTH (50% of patients with small-cell carcinoma), although Cushing's syndrome is rare with bronchogenic carcinoma. Tumors appear to elaborate both active ACTH (in small amounts) and an immunoreactive, but biologically weak *big* ACTH, which can be a precursor molecule. Big ACTH was evaluated as a marker for lung cancer, because it is present in more than 80% of all patients who have lung cancer. It is not, however, specific, because it also occurs in a significant number of patients with chronic obstructive pulmonary disease. When Cushing's syndrome does occur in association with tumor ACTH secretion, it is a virulent disease with poor prognosis. Ketoconazole, an inhibitor of adrenal steroid synthesis secondary to its inhibitory effects on the cytochrome P-450 enzyme system, has been reported to significantly suppress serum cortisol levels in a patient with Cushing's syndrome caused by small-cell carcinoma.

Hypercalcemia occurs in at least 12% of patients with lung cancer, mainly with epidermoid carcinomas. Although small-cell carcinoma frequently metastasizes to bone,

it rarely causes hypercalcemia. Ectopic parathyroid hormone production is one cause of hypercalcemia that usually responds to therapy. Some cases may be caused by tumor-secreted prostaglandin E. The hypercalcemia in these patients can be suppressed by aspirin or indomethacin. Other cases may be caused by tumor production of a peptide with significant structural homology to parathyroid hormone, but without immunologic cross-reactivity.

The syndrome of inappropriate ADH (SIADH) results from ectopic ADH secretion. It occurs in 11% of patients with small-cell carcinoma and, although hyponatremia can be severe, symptoms occur in only approximately 25% of patients with tumor-induced SIADH. It usually resolves within 3 weeks of the initiation of chemotherapy. Occasionally, severe SIADH can occur in the first 5 days following the start of chemotherapy, thus, patients should be monitored carefully during this time. Preliminary studies have used ^{131}I-labeled antibodies against vasopressin-associated neurophysin to localize tumors using radioimaging.

Other causes of hyponatremia associated with lung cancer are much less common. Renal tubular dysfunction in association with glycosuria and aminoaciduria has been reported, as has sodium loss associated with massive bronchorrhea in bronchoalveolar cell carcinoma. In addition, some hyponatremic patients with lung cancer who have normal levels of ADH have been found to have increased messenger RNA levels for atrial natriuretic factor as a possible mechanism for their deranged sodium homeostasis.

Gonadotropin production occurs predominantly with large-cell carcinoma and can cause gynecomastia, which can be unilateral. Prolactin production by anaplastic tumors can cause lactation in women. Rarely, epidermoid carcinomas have been associated with the production of vasoactive intestinal peptides, resulting in a syndrome of watery diarrhea, hypokalemia, and achlorhydria. In addition, bronchogenic carcinomas have been found to produce small, biologically active amines or peptides, including serotonin, histamine, and a substance resembling eosinophilic chemotactic factor of anaphylaxis.

Currently, most of these hormones represent curiosities. In the future, some may become useful markers of disease or response to therapy, and the mechanisms of their production may provide insights into the behavior of carcinoma.

A retrospective study of 40 years of reports in the literature found that 13% of patients with resectable non–small-cell lung cancer had a paraneoplastic syndrome. The authors suggested that recent onset arthritis and arthralgias, without other explanations, should be considered as early clues to possible lung cancer. Increasing recognition of new paraneoplastic syndromes, many of which are felt to be immunologically mediated, has been accompanied by frequently disappointing trials of therapy with steroids, immunoglobulins, and plasmapheresis. Ongoing study of immunoadsorption with protein A for paraneoplastic neurologic syndromes has shown some initial success and merits further trials.

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107. SOLITARY PULMONARY NODULE

Henri G. Colt

A solitary pulmonary nodule (SPN) is defined as *a well-circumscribed spherical lesion* that is completely surrounded by aerated lung and not associated with atelectasis or adenopathy. Often inappropriately referred to as *coin lesions*, SPNs are not pleural or mediastinal based. Although no consensus exists as to the upper limit of size, most authors agree that true SPNs are less than 3 cm in diameter, differentiating SPN from the solitary mass lesion, which has a greater likelihood of being malignant. Much effort has been spent trying to determine which SPNs can be safely observed and which require diagnostic interventions or thoracotomy with resection.

Cancer or granulomatous disease (e.g., tuberculosis, coccidioidomycosis, and histoplasmosis) causes most SPNs. Bronchogenic carcinoma presents as SPN in 10% to 20%

of instances. Most of these are adenocarcinomas, although squamous cell carcinoma, bronchioalveolar cell carcinoma, carcinoid tumors, and even small-cell carcinomas can also present as SPNs. Approximately 5% of SPNs represent metastasis from colon, breast, kidney, testicle, bone sarcoma, or malignant melanoma. These findings have prompted the *when in doubt, cut it out* approach to SPNs and underscore the importance of prompt evaluation and management, especially in patients with risk factors (e.g., smoking) or a previous history of cancer.

Benign SPNs are usually granulomatous from tuberculosis or fungal infections. *Pneumocystis carinii* infection can also appear nodular, as can viral infections (e.g., cytomegalovirus). Less common causes include resolving pneumonia, pulmonary infarction, lung abscess, hamartomas, Kaposi's sarcoma, pulmonary arteriovenous malformation, pulmonary contusion, pulmonary sequestration, Wegener's granulomatosis, mucoid impaction, and bronchogenic cysts. Although more than 50% of SPNs are benign, the *watchful waiting* approach is usually not adopted before completing careful examination of imaging studies and analysis of the nodule's probability for malignancy. Bronchoscopic or percutaneous diagnostic procedures are usually indicated. Patients must be encouraged to participate in the decision-making process.

Four clinical features are usually cited that increase the likelihood of a benign SPN: (1) absence of growth of the nodule over a 2-year period; (2) absence of risk factors for cancer; (3) presence of calcium in characteristic patterns on imaging studies; and (4) age less than 35 years. Nonsmoking, younger patients living in areas endemic for fungal disease are more likely to have benign nodules. Risks for malignancy increase with age, smoking history, and nodule size, although the probability for malignancy cannot be accurately based on any single characteristic. A careful history and physical examination are essential and should include smoking and occupational history, history of cancer, and careful inquiry regarding the patient's known place of residence and travel (especially those who travel to areas endemic for histoplasmosis or coccidioidomycosis). Unexplained hypoxemia may suggest arteriovenous malformation. Pulmonary function studies help to assess the potential risk of thoracotomy. Sputum cytology is usually not helpful. Skin tests and serologies can be helpful if tuberculosis or fungal diseases are suspected, especially in endemic areas.

Initial assessment of an SPN is usually made on examination of the posteroanterior and lateral chest radiograph. Unfortunately, the shape, location, and margins of the lesion or the presence of cavitation are unreliable for differentiating malignant from benign SPNs. Lobulation and larger size tend to be associated with malignancy, although these characteristics are not definitive. Only two features—calcification and growth rate—can be used with some degree of confidence. An SPN can be assumed to be benign if calcifications fit one of four distinct patterns: (1) central calcification; (2) ring or halo pattern; (3) diffusely speckled calcification; or (4) dense, irregular pattern termed *popcorn calcification*. Comparison of recent chest radiographs with previous ones is necessary and very helpful. Up to 10% of SPNs may be seen only on or better on the lateral view. Fluoroscopy can be used to differentiate SPN from other opacities (e.g., a nipple shadow). Computed tomography (CT) scans, particularly thin-section studies, have been shown to be cost-effective and of greater sensitivity than conventional tomography. If no calcifications are seen on CT, nodule density compared with a densitometry phantom (density ~ 185 Hounsfield units) may help to detect calcifications in otherwise indeterminate nodules. For example, up to 25% of hamartomas will have CT evidence of calcification. In addition, many hemartomas are partially composed of CT-visible fat-density tissue. Small, eccentric calcifications within a SPN do not ensure benignity because this pattern can be found in scar carcinoma.

If malignancy is suspected, the CT scan will also assist in staging the mediastinum and upper abdomen. CT is more sensitive than chest x-ray study and may identify multiple pulmonary nodules when only one is suspected from chest radiographs. Chest CT, therefore, should be performed in patients with a SPN who are candidates for cancer resection, particularly if resection of known metastatic nodules is being considered. Recent reports suggest that low-dose spiral or helical CT (single breath hold, entire lung volume scanning) techniques provide an opportunity to diagnose lung cancer at an early stage. The potential of using spiral CT in addition to sputum cytology for early lung cancer screening is promising. Another exciting diagnostic modality is dynamic positron

emission tomography (PET). The sensitivity and specificities of this noninvasive diagnostic modality in detecting lung cancer are in the 85% to 95% range. Differentiation of benign from malignant lesions is achieved by qualitative or quantitative analysis of glucose metabolism of tissues. Results depend, however, on the generation of scanner used, and a long learning curve is required to assess results correctly.

Management goals in patients with SPN include limiting the number of unnecessary thoracotomies for benign disease and expediting potential curative lung resection in patients with malignancy. Much controversy persists, however, regarding optimal diagnostic evaluation. Some decision analysis studies suggest watchful waiting when the probability for malignancy is less than 5% or the risk of surgery is high. Again, the importance of risk factors (e.g., smoking or asbestos exposure) or the presence of systemic symptoms possibly related to cancer (e.g., weight loss, hemoptysis, new cough, or change in the pattern of chronic cough) must be emphasized. Although specific symptoms may not be caused by the SPN *per se*, radiographically occult processes may be discovered. A careful physical examination to exclude melanoma or testicular carcinoma is important before adopting a conservative approach. When the watchful waiting approach is advocated, repeat chest radiographs should probably be obtained at least every 2 to 3 months for the first year.

Although survival appears inversely proportional to nodule size, no studies have demonstrated decreased survival with a few months of careful observation. Therefore, management decisions can probably be safely postponed until old radiographs or CT scans are obtained for review. Patients with recent chest-wall trauma or pneumonia may warrant a few weeks of observation to see if lesions resolve. If a lesion has been stable for 2 or more years, further diagnostic evaluation probably can be avoided unless the patient is symptomatic.

Moving from a *watchful waiting* approach toward intervention is often based on change in appearance or growth of the SPN. The growth rate of a SPN can be determined by measuring its doubling time (DT), which refers to doubling of volume, not diameter. DT is derived from the formula for a sphere: $V = 4r^3$, where V = volume and r = radius. A very slow (>2 years) or very fast (<7 days) DT suggests benignity. Growth assessment, however, is difficult. For example, a 1-cm nodule that doubles in volume would only increase 26% in diameter.

Tissue diagnosis usually requires flexible bronchoscopy or percutaneous procedures. Bronchoscopy with washings, brushings, and biopsy under fluoroscopic guidance has a yield of 40% to 80%, but complications are infrequent (<2%). Yield decreases when nodules are less than 2 cm in diameter. A *positive bronchus* sign (evidence of a bronchus leading to the nodule) seen on CT scan may indicate a higher diagnostic yield for bronchoscopy. Bronchoscopy also allows airway inspection and detection of otherwise unrecognizable endobronchial disease. Yield is increased by using transbronchial needle aspiration (TBNA).

Percutaneous procedures include transthoracic needle aspiration (TTNA) under fluoroscopic, ultrasound, or CT guidance. Yield is greater (80% to 95%), but so are complications (pneumothorax in 25%). Also, false-negative results can occur in up to 30% of cases. A central location and lung hyperinflation increase the risk of pneumothorax. TTNA is particularly helpful in smaller peripheral nodules that are more difficult to reach by bronchoscopy and with a strong suggestion of a granulomatous cause. If a malignancy is diagnosed by TTNA, bronchoscopy should probably be performed, especially if the chest x-ray study or CT scan suggests enlarged lymph nodes, to evaluate the central airways and to sample mediastinal nodes. Tumor can be diagnosed in up to 50% of enlarged nodes by bronchoscopic needle aspiration, thereby sparing some patients a thoracotomy. Overall, many experts believe that bronchoscopic needle aspiration is underutilized, probably because of insufficient exposure to the procedure during pulmonary specialty training.

Immediate thoracotomy for a SPN has been advocated as an alternative approach, although some risk is seen in resecting a SPN, with surgical mortality reported as high as 4% in patients at higher risk. In carefully selected patients, video-assisted thoracoscopic surgery (VATS) may be warranted, but precise manual palpation of lung parenchyma is not possible and nodules not seen on CT scan can be missed. In some instances, CT or ultrasound guidance is used for guidewire insertion that facilitates

thoracoscopic detection. When compared with bronchoscopy or percutaneous needle aspiration, thoracoscopy is virtually 100% sensitive and 100% specific, offering an excellent, albeit expensive alternative. Additional prospective studies comparing thoracoscopic wedge resection with standard resection by thoracotomy for cure of bronchogenic carcinoma are necessary before VATS is generally adopted for anything more than diagnosis. Nevertheless, many agree that, in experienced hands, a VATS approach is associated with less postoperative pain than traditional thoracotomy. Also, stapled lobectomy for curative resection is possible and easily combined with lymph node sampling.

Three clinical situations demand special consideration. First, in patients without tissue diagnosis after bronchoscopy and TTNA, cancer cannot be excluded, and it is probably best to proceed to resection. If surgical risk is high or the suspicion of malignancy is low, lesions can be followed by serial chest radiographs at least every 2 to 3 months for 1 year and every 4 to 6 months for the second year or longer until any suspicion that the nodule is a slow-growing malignancy has been alleviated. Informing patients and families of all diagnostic and therapeutic options and encouraging their participation in the clinical decision-making process are essential.

The second situation is when a biopsy or needle aspiration reveals small-cell carcinoma presenting as a SPN. Although uncommon, small-cell carcinomas presenting in this fashion appear to have a better prognosis than the standard type. Stage I tumors have had a 5-year survival rate of 35% when treated by resection alone. Before surgical resection, however, the possibility of distant metastasis must be excluded. Postoperative adjuvant chemotherapy has also been advocated.

The third special situation is when a SPN occurs in a patient with a history of malignancy. Tissue diagnosis is usually required because conclusive evidence of metastatic disease will dictate further therapy. Pulmonary metastasectomy favorably influences survival, especially in patients with soft tissue sarcoma or melanoma. In patients with a history of cancer, a SPN should never be presumed to be a metastatic lesion. Indeed, a 50% likelihood is seen that a new SPN is either benign or a distinct treatable primary malignancy. Metastatic disease is more likely if (1) the known primary tumor is an adenocarcinoma; (2) the lung lesion appears within 12 months after treatment of the primary tumor; (3) the patient is young and a nonsmoker; and (4) the primary tumor was associated with metastatic lymphadenopathy. In the absence of known extrapulmonary malignancy, the SPN will prove to be a metastasis in less than 5% of cases.

Patients undergoing pulmonary metastasectomy have a 5-year survival rate of 20% to 30% so long as the primary tumor has been controlled and no other evidence is seen of other metastases.

The prognosis of bronchogenic carcinoma presenting as a SPN, particularly T1N0M0 disease, is very good, justifying a vigorous diagnostic approach in patients at high risk.

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108. MEDIASTINAL MASS

Stephen P. Bradley

A variety of benign and malignant processes can present as a mediastinal mass. The differential diagnosis requires knowledge of normal mediastinal anatomy. The mediastinum can be divided into three compartments based on the lateral chest radiograph. The *anterior mediastinum* is bounded by the thoracic inlet superiorly, the sternum anteriorly, and the anterior pericardium posteriorly. It contains the upper esophagus and trachea, thymus, aortic arch, adipose tissue, and lymphatics. The *middle, or visceral, mediastinum* holds the pericardium and its contents, the low trachea, carina and main bronchi, and associated lymph nodes. The *posterior mediastinum* reaches from the posterior pericardium to the anterior vertebral column and posterior ribs, including the paravertebral gutters. It contains the esophagus, descending aorta, sympathetic ganglia, and peripheral nerves.

The differential diagnosis is based primarily on the location of the mediastinal mass. Approximately one half of mediastinal masses arise in the anterior compartment. These include thymomas, germ cell neoplasms, Hodgkin's and non-Hodgkin's lymphomas; cysts of pericardial, bronchogenic, or thymic origin; and intrathoracic goiters. Much less common are mesenchymal tumors (lipomas, fibromas, lymphangiomas, hemangiomas, cystic hygromas, and their malignant counterparts), carcinoma of unknown primary, and angiofollicular lymphoid hyperplasia (Castleman's disease).

Mass lesions of the middle mediastinum (18% to 25% of total) include pericardial, bronchogenic, or enteric cysts; lymphomas, granulomatous lesions (tuberculosis, sarcoidosis, or histoplasmosis), carcinoma, and mesenchymal tumors. Metastatic carcinoma to the middle mediastinum is frequent, but in almost all cases the site of the primary tumor is apparent.

Of the 23% to 27% of mediastinal masses that arise in the posterior compartment, approximately three fourths are neural in origin. Other mass lesions of the posterior mediastinum include cysts, alimentary tract duplications, intrathoracic thyroid, pheochromocytomas, and ectopic thymus.

The most common mediastinal tumors vary from series to series. In children, neural tumors lead in frequency (33%), followed by lymphomas (14%), teratomas (10%), thymic masses (8.5%), bronchogenic cysts (7.5%), enteric cysts (7.0%), angiomatous tumors

(6.8%), and inflammatory nodal masses (4.4%). The frequency of malignancy in mediastinal mass lesions in children (up to age 16) is approximately 50%.

Large series involving mostly adult patients report widely varying frequencies of different mediastinal lesions. By combining 13 reported studies involving 2399 patients, the following mean (and range) percentage rates for mediastinal lesions are derived: neurogenic tumors, 20.7% (14% to 36%); thymoma, 19.1% (10% to 27%); cyst, 18.3% (0 to 26%); lymphoma, 12.5% (5% to 23%); germ cell neoplasm, 10.0% (5% to 29%); endocrine tumor, 6.4% (0 to 23%); mesenchymal tumor, 6.0% (0 to 11%); primary carcinoma, 4.6% (0 to 23%); and miscellaneous masses, 2.4% (1% to 14%).

Approximately half of mediastinal masses are discovered incidentally on chest roentgenogram. Malignant lesions of all types are much more likely to be symptomatic on presentation than benign lesions. Signs and symptoms, which usually result from a mass effect on surrounding structures, include dyspnea, cough, wheezing, hemoptysis, chest pain, dysphagia, superior vena cava syndrome, and Horner's syndrome. Neural tumors with an intraspinal component (dumbbell tumors) can cause cord compression.

The appearance of a mediastinal mass on posteroanterior and lateral chest roentgenograms can narrow the differential diagnosis by localizing the lesion to a certain mediastinal compartment. Computed tomography (CT) is useful in more precisely localizing and defining the extent of the mass and can help determine the best approach for biopsy. With some masses (e.g., intrathoracic goiter and mature teratomas), a confident diagnosis can be made based on CT findings. When intravenous contrast is used, CT scanning can distinguish vascular lesions (e.g., congenital vascular rings, enlarged pulmonary arteries, double vena cavae, and aortic aneurysms) that can mimic mediastinal masses. Other masqueraders that can usually be ruled out by CT include diaphragmatic hernias, anterior meningoceles, and pulmonary lobar sequestration. The primary role of magnetic resonance imaging (MRI) has been as a problem-solving device, especially when results of CT have been equivocal. Advantages of MRI include the lack of ionizing radiation, the ability to image in virtually any plane (useful when imaging masses in the aorticopulmonary window and paraspinal areas), and the ability to differentiate blood vessels from soft tissues without the use of intravenous contrast. In addition, MRI is the imaging technique of choice in evaluating posterior mediastinal masses thought to be neurogenic because it can determine whether there is extension into the spinal canal, precluding the need for a myelogram. Other imaging techniques such as ^{131}I thyroid scintigraphy, barium esophagography, and angiography have largely been replaced by CT scanning.

The radiographic appearance of a mediastinal mass rarely provides a diagnosis; additional procedures are usually required. With anterior mediastinal masses, testing of serum β-human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) (for germ cell tumors) and antiacetylcholinesterase receptor antibodies (for thymomas) may be useful. The results of transthoracic fine-needle aspiration vary between series. The sensitivity for diagnosing malignancy is reported to be as high as 90%, but a precise tissue diagnosis is made in only 60% to 80% of patients. The diagnosis of lymphoma and thymoma can be particularly difficult on fine-needle aspiration specimens. Cervical mediastinoscopy (for anterior mediastinal masses) and anterior thoracotomy (for masses in the aorticopulmonary window) can often provide sufficient tissue for a specific diagnosis. Bronchoscopy with transcarinal needle aspiration is occasionally successful in diagnosing subcarinal masses. Thoracoscopy (video-assisted thoracic surgery) is used in some centers to diagnose and, occasionally, resect masses in all three mediastinal compartments.

The purpose of the aforementioned procedures is to provide a diagnosis (e.g., lymphoma, seminoma, or metastatic carcinoma) for which resection is not the primary treatment modality. In the remaining patients, diagnosis is made at exploratory thoracotomy, thoracoscopy, or median sternotomy. Caution must be used when subjecting patients with large mediastinal masses to general anesthesia. These patients are at risk of developing airway compromise because of tracheobronchial compression. The greatest risk is in children, in whom the degree of respiratory symptoms is not a reliable predictor of the degree of tracheobronchial compromise. For patients in whom preoperative CT scan demonstrates greater than one third compression of the airway, it may be necessary to avoid the supine position, use spontaneous ventilation, and occasionally perform cardiopulmonary bypass.

From 20% to 30% of neural tumors are malignant; three fourths of these occur in children. Thus, adult neural tumors are almost all benign. In adults, the most common neural tumors are schwannomas (neurilemomas), which arise from the Schwann's cells that sheath nerve cell axons, and neurofibromas, which arise from nerve sheath fibrous tissue. Rarely, malignant degeneration of both schwannomas and neurofibromas can occur; prior irradiation or neurofibromatosis each increases the risk. In contrast, most (50% to 60%) neural tumors in children are malignant. Neuroblastomas, arising from peripheral nerve cells, are the most frequent mediastinal tumor in children. These highly aggressive tumors are usually diagnosed in children before age 3. Ganglioneuromas (benign) and ganglioneuroblastomas (malignant) arising from sympathetic ganglia are also common in children. Greater than 50% of neural tumors are found incidentally on chest radiograph. Rib and vertebral changes seen on x-ray film may be caused by pressure phenomena and do not necessarily connote malignancy. Benign neural tumors are treated definitively by surgical excision; dumbbell tumors require combined thoracotomy and laminectomy as a one-step operation. Postoperative radiation therapy is given for malignant lesions.

Mediastinal developmental cysts are nearly always benign and, except in infants and young children, are usually asymptomatic at presentation. Bronchial cysts are most often found in the middle mediastinum near the tracheal bifurcation but can be found in all three compartments. They rarely communicate with the tracheobronchial tree. Pericardial cysts typically occur in the anterior cardiophrenic angle, most often on the right. A small minority communicate with the pericardial space. Esophageal cysts, the least common, are found in either the posterior or middle mediastinum. Because two thirds of patients with foregut (bronchial and esophageal) cysts eventually develop symptoms, surgical resection is usually recommended; pericardial cysts rarely become symptomatic.

Thymomas are the most common anterior mediastinal mass. Four cell types are seen: lymphocytic, epithelial, spindle, and mixed. Malignancy is defined by tumor invasiveness at surgery, not by cell type. Benign thymomas (55% to 65% of total) are contained within a thick fibrous capsule; surgical removal is considered curative, although 2% to 12% recur, necessitating long-term radiographic follow-up. Invasive (or malignant) thymomas are defined by invasion through the capsule and typically spread locally. Therapy consists of surgical excision (if possible) and postoperative radiation therapy. Prolonged survival in patients with locally advanced disease has been described, emphasizing the indolent nature of these tumors. Parathymic syndromes occur in up to 50% of patients with benign or invasive thymoma. Myasthenia gravis occurs in 30% to 50% of all thymomas (15% of patients with myasthenia gravis have thymoma); resolution after thymectomy occurs in approximately 25% of patients, particularly in young women. Thymomas have also been associated with pure red cell aplasia (5% of patients), and hypogammaglobulinemia (10%). Thymic carcinoma (distinguished by cellular atypia, early local invasion, and distant metastases), thymic carcinoid, thymolipoma, and thymic cysts are uncommon causes of anterior mediastinal masses.

Nodular sclerosing Hodgkin's disease is the most common lymphomatous lesion confined to the mediastinum. These patients often have massive mediastinal adenopathy; they are treated with combined radiation therapy and chemotherapy, thereby obviating the need for staging laparotomy and the risk of airway compromise. Nodular sclerosing Hodgkin's disease carries a favorable prognosis. Non-Hodgkin's lymphoma (lymphocytic, histiocytic, mixed) is associated with a poorer prognosis, despite the use of aggressive chemotherapeutic regimens.

The anterior mediastinum is the most common extragonadal site for *germ cell neoplasms*, which are most common in the third decade of life. They can be divided into dermoids (only an epithelial layer present) and teratoids (all three germ layers present). Of dermoids, 10% to 15% are malignant as are 15% to 40% of teratomas. Dermoids are usually cystic; teratomas can be cystic (usually benign) or solid (usually malignant). Surgical excision is curative for benign germ cell tumors. Greater than 90% of malignant teratomas (seminoma, teratocarcinoma, embryonal cell carcinoma, entodermal sinus tumors) occur in men. Choriocarcinomas are associated with gynecomastia in at least half of cases and with tumor production of HCG in 100% of cases, whereas AFP is present in 97% of entodermal sinus (yolk sac) tumors. Low levels of HCG are

produced by approximately 10% of seminomas. Results of therapy for mediastinal germ cell tumors have improved significantly with the use of aggressive combination chemotherapy; surgical excision of residual tumor is often performed.

A syndrome of poorly differentiated carcinoma occurring in young men with mediastinal masses has been described. Serum assays for HCG and AFP are often negative; however, further evaluation has revealed that a subset of these patients have extragonadal germ cell tumors and respond to appropriate chemotherapy.

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109. NEOPLASTIC DISEASE OF THE PLEURA

Henri G. Colt

Neoplastic disease of the pleura can be primary, arising from the cellular elements of the pleural surface (e.g., mesothelial tissue), or metastatic, arising from either thoracic or extrathoracic sites. Metastatic pleural tumors comprise most pleural neoplasms, histologically resemble the primary tumor, and are usually associated with a roentgenographically apparent effusion or pleural thickening.

Primary tumors of the pleura are rare and are classified as benign mesotheliomas (i.e., *solitary* or *localized* fibrous) and diffuse malignant mesotheliomas. Solitary fibrous tumors of the pleura occur equally in men and women with a peak incidence in the fourth to sixth decades. The tumor is grossly well encapsulated and histologically composed of fibrous elements. The cause is unknown, but similar lesions have been reported as *postinflammatory tumors* of the pleura, leading to speculation that they are part of a spectrum of mesothelial cell response to a variety of stimuli. Immunohistochemical, ultrastructural, and tissue culture studies previously were felt to support a mesenchymal origin, but most agree now that these tumors are derived from fibroblasts and have the potential for multidirectional differentiation. Tobacco smoking and exposure to asbestos do not appear to increase the risk for any of these tumors.

Clinically, 30% to 40% of patients with these tumors are asymptomatic at the time of diagnosis; others complain of chest pain, cough, dyspnea, and weight loss in decreasing frequency. The tumors can reach an enormous size. They can be attached to the pleura by a pedicle and lead to a sensation of something moving about in the chest after a positional change. Rarely, they cause lobar collapse or superior vena caval obstruction. Other times, they present as wide-based parietal pleural abnormalities noted on chest radiographs or computed tomography (CT) scans. Infrequently, tumors involve the visceral pleural surface, presenting radiographically as solitary pulmonary nodules.

The physical examination is usually unrewarding but may show evidence of pleural effusion, clubbing (<20%), or osteoarthropathy or arthropathy (<15%), simulating rheumatoid arthritis. The chest roentgenogram usually reveals a localized mass; pleural effusion occurs in less than 15% of cases. In some large tumors, hypoglycemia has been reported. Although needle biopsy, pleural fluid cytology, or pleural biopsy may suggest the diagnosis, the definitive diagnosis of solitary fibrous tumors of the pleura usually requires thoracoscopy or thoracotomy. Preoperative differential diagnoses include malignant mesothelioma, metastatic carcinoma, sarcomas, and bizarre pseudotumors related to the organization of a pleural exudate. Surgical resection is usually curative but can be difficult in cases of gross invasion of contiguous vascular, neural, or mediastinal structures. Recurrences may not appear for years following initial resection. Often, the arthropathy disappears with tumor resection but can recur with regrowth. It can then be relieved by further resection.

The most common primary pleural neoplasm is a mesothelioma. It must be distinguished from other neoplasms, such as soft tissue sarcoma and leukemia or lymphoma involving the pleura. Mesothelioma is rare, accounting for less than 1% of all cancer deaths in the general population; however, its incidence is rising because of (1) the delayed effects of an increase in the occupational exposure to asbestos; (2) an increased awareness by pathologists of this disease; and (3) more accurate diagnostic methods, such as electron microscopy and immunohistochemistry. Today, it is felt that approximately 2000 cases are diagnosed yearly in the United States.

Malignant mesotheliomas also occur as primary tumors of the peritoneum and tunica vaginalis of the testes; simultaneous occurrence of pleural mesothelioma with mesothelioma at these other sites has not been described, although patients may have both pleural and peritoneal involvement during the course of their illness. Pathologically, this tumor appears early as single or multiple, small, white or gray lesions; later it may produce a thick, gelatinous, gray–pink sheath enveloping the affected lung. It is noteworthy that thoracoscopic appearance can be misleading. Parietal pleura can appear normal, as is often the case in stage 1A malignant mesothelioma, or appear as a conglomeration of small or large nodules involving parietal, visceral, or both pleural surfaces.

Histologically, tumors are composed of epithelial and mesenchymal (fibrosarcomatous) elements and are classified as epithelial (54%), fibrosarcomatous (21%), or mixed (25%). Epithelial mesotheliomas are the most frequently diagnosed histologic type. Seven types of epithelial mesotheliomas are seen, the most common of which is the tubulopapillary pattern. Sarcomatoid mesotheliomas, which account for approximately 20% of mesotheliomas, are usually positive on keratin staining, contrary to most sarcomas. Of epithelial mesotheliomas, 20% produce hyaluronic acid, which can be identified by specific stains. The presence of hyaluronic acid contributes to the increased viscosity often noted in pleural fluid from patients with mesothelioma. Carcinoembryonic antigen (CEA) has been reported as negative in 88% of mesotheliomas. This immunostaining procedure can

be helpful in excluding mesothelioma from the diagnosis. Immunohistochemical and ultrastructural analysis of pleural neoplasms can lead to an accurate diagnosis of mesothelioma in most cases, although a careful review of an entire battery of tests often including CEA, *Leu*-M1, and mucicarmine staining, is necessary. Electron microscopy can be helpful when abnormalities such as long slender microvilli are noted. On rare occasions, diagnosis can only be made retrospectively, after review of the exposure history, clinical history, immunohistochemical stains and ultrastructural analyses, clinical and radiographic progressions of disease (usually one of gradual entrapment of the lung with associated pleural thickening, and dyspnea), and autopsy findings.

Although the pathogenesis of malignant mesothelioma is unclear, asbestos is the single most important causative agent. This conclusion is based on (1) retrospective studies showing a strikingly higher incidence (300×) of malignant mesothelioma among asbestos workers; (2) studies showing a significantly higher incidence of asbestos exposure among new mesothelioma cases versus controls; and (3) direct measurements of significantly increased asbestos fiber content of the lungs of patients with mesothelioma (95%) with respect to controls. A threshold amount of asbestos exposure necessary to induce mesothelioma is unknown but presumed. Cigarette smoking is not a risk factor for malignant mesothelioma, but the addition of smoking to that of asbestos exposure significantly increases the risk for lung cancer.

Asbestos exposure can occur occupationally, as in textile, shipyard, mining, insulation, and construction industries, or it can occur environmentally, as with persons living near asbestos mines and mills. Significant exposure can also occur when family members of asbestos workers handle the workers' clothing (paraoccupational). Thus, the level of exposure may seem inconsequential and the fiber burden may be less than expected to cause asbestosis. Fiber size can be important in that fibers that are long and thin have been found to be more tumorigenic than shorter, thicker fibers, although all types of asbestos can induce mesotheliomas. The various types of asbestos vary in tumorigenicity. Fibers with the longest length:diameter ratio are the most carcinogenic. It appears that amphiboles, particularly crocidolite (but also amosite, anthrophyllite, tremolite, and actinolite), are more frequently associated with malignancy than serpentine fibers such as chrysotile asbestos.

A direct relationship exists between intensity and duration of exposure with tumor incidence. Intensity of exposure is related inversely to time of presentation. The mean time between exposure and presentation (latency period) is approximately 29 years for factory workers and 48 years for those exposed environmentally. Asbestos fibers are inhaled and deposited at the level of smaller bronchioles and alveoli, where they are ingested by pulmonary alveolar macrophages and coated with a ferrous proteinaceous material. Asbestos fibers are believed to be both promoters and initiators of malignant transformation. Once inhaled, asbestos fibers cannot be destroyed or removed; thus, the lifetime risk for mesothelioma increases over time.

Other nonasbestos causes of mesothelioma are also seen, including naturally occurring fibrous silicate minerals called *erionite*, a fibrous zeolite. Individuals living in small villages in central Turkey where this mineral was used in building materials have had the highest incidence of mesothelioma in the world. Most artificial fibers (e.g., ceramic fibers, glass wool, and rock wool) have not been shown to cause mesothelioma.

In contrast with patients with solitary fibrous tumors of the pleura, almost all patients with malignant mesothelioma are symptomatic at the time of diagnosis, although presentation as an incidental radiographic finding of pleural effusion is increasingly common. Chest pain (43%) of a constant *gnawing* character is a frequent complaint. Occasionally positional, it is rarely pleuritic in nature. Dyspnea is another frequent symptom (27%), with or without chest pain at presentation. Cough (19%), weight loss (13%), and fever (7%) also occur. Weight loss is a poor prognostic sign.

The physical examination frequently reveals evidence of pleural effusion. Clubbing is infrequent (<5%). Auscultation of the chest may reveal decreased breath sounds unilaterally, coarse crackles, squeaks, or pleuropericardial rubs. Horner's syndrome, hoarseness, or tumor extending through the chest wall in the tract of a previous needle tract or incision site are infrequently noted today. The chest roentgenogram typically reveals either a unilateral pleural effusion, pleural nodularity or thickening, or a localized mass lesion. A massive effusion without mediastinal shift away from the

side of the fluid collection should raise suspicions for mesothelioma, especially with a history of asbestos exposure. Rib destruction may be present adjacent to the pleural lesion. Interstitial fibrotic changes or diaphragmatic pleural calcifications suggest prior asbestos exposure and are not indicative of malignant pleural mesothelioma. CT scan may demonstrate pleural calcifications, a distinct pleural mass, invasion of contiguous structures, or abdominal extension not otherwise apparent radiographically.

The tissue diagnosis of malignant mesothelioma can be difficult. Sputum cytology is negative, and bronchoscopy usually reveals no endobronchial lesions, although extrinsic bronchial compression caused by mediastinal pleural thickening, a large pleural effusion, or entrapped lung with volume loss is observed occasionally. The pleural fluid from a thoracentesis is usually straw-colored but can be serosanguinous or bloody in 30% to 50% of cases. Typically, the protein level is elevated, ranging from 3.5 to 5.5 g/dl and lactic acid dehydrogenase is high. An elevated concentration of hyaluronic acid has been observed by some investigators; however, it appears to be neither specific nor sensitive for the diagnosis of mesothelioma. The value of pleural fluid cytology is controversial, although many experts believe that cytology is of limited value because benign and malignant mesothelial cells closely resemble each other.

Closed pleural biopsy using a Cope, Abrams, or Trucut biopsy needle may confirm the diagnosis but usually provides insufficient tissue. Thoracoscopy, on the other hand, allows complete evacuation of pleural effusion, thorough examination of parietal and visceral pleural surfaces, assessment of lung expandability, and visually guided biopsy of both normal and abnormal appearing areas of the costal and diaphragmatic parietal pleura. Procedures are almost always diagnostic. In addition, if intrapleural chemotherapy is not planned, patients can simultaneously undergo thoracoscopic talc pleurodesis, which is successful in preventing fluid reaccumulation in more than 80% of instances. Rarely, open thoracotomy is necessary for definitive diagnosis, but should probably not be performed unless an open parietal pleural biopsy has been unsuccessful. Sometimes, even after the removal of substantial tissue mass, the pathologist has great difficulty in making a diagnosis.

Major differential diagnoses include adenocarcinoma of the lung, bronchoalveolar cell carcinoma, and metastatic pleural tumors (especially from the pancreas, gastrointestinal tract, and ovary). Of course, mesothelial cell proliferation from benign inflammatory processes also need to be excluded. The histologic distinction for metastatic adenocarcinoma, at times, is so difficult that diagnosis is based on exclusion of another primary tumor, as well as the gross appearance of the pleural tumor at thoracoscopy or surgery. Electron microscopy can be useful, particularly in excluding bronchoalveolar cell carcinoma and adenocarcinoma from the lung, breast, and upper gastrointestinal tract.

Malignant mesothelioma is an unrelenting, progressively fatal disease. Aggressive surgical resection, radiation therapy, and chemotherapy have all yielded poor results. Newer regimens using combined treatment modalities are under evaluation but have yet to alter the grim prognosis. Novel gene therapy protocols, although initially promising, are still in the experimental stage and have not been shown to alter outcome significantly.

As disease progresses, patients may present with obstruction of the superior or inferior vena cava (or both) or pericardial involvement. Involvement of the soft tissues of the chest cage, ipsilateral lung, contralateral pleura, supraclavicular nodes, and peritoneal cavity is also seen. Distant metastases to bone, liver, or brain rarely occur. The average survival time in most series of mesothelioma is 6 to 12 months after diagnosis and 8 to 14 months after the onset of symptoms.

Metastatic pleural involvement (increasingly referred to as *pleural carcinomatosis*) is the most common form of neoplastic pleural disease. It usually presents as a pleural effusion that can be pathogenically related to visceral or parietal pleural implants, peripheral or mediastinal lymphatic and venous obstruction, thoracic duct obstruction, or a combination of these mechanisms. Tumor lymphatic obstruction, thoracic duct invasion, or both can also result in chylothorax. It is noteworthy that chylothorax is not necessarily *milky* in appearance.

Metastatic pleural carcinomatosis is responsible for 50% of all pleural effusions. The most common neoplastic sources are primary lung (33%), especially adenocarcinoma and undifferentiated cell, breast (21%), and stomach (7%). Other less frequent primary

tumors are those of the ovary, pancreas, liver, kidney, uterus, adrenal glands, testis, larynx, and thyroid. In addition, benign pelvic tumors can be associated with a pleural effusion and ascites (Meigs–Salmon syndrome) that subside following tumor resection.

The pathogenesis of metastatic malignant pleural disease is unclear. Metastatic tumor deposits without pleural effusion are frequently noted at postmortem examinations in patients dying from malignancy; unless extensive, they are clinically undetectable on radiographs or CT scans, although pleural thickening may be noted. These deposits are felt to result from hematogenous spread. The lack of accompanying effusion has prompted some authors to emphasize the role of lymphatic obstruction in the pathogenesis of malignant effusion. In fact, a frequent finding during thoracoscopic inspection of the parietal pleura is swollen lymphatics, particularly along the posterior and inferior costal parietal pleura.

The clinical manifestations of metastatic pleural tumors relate to the primary neoplastic process and the size of the effusion. Dyspnea can be severe if a large amount of fluid accumulates. Roentgenographically, the findings of mediastinal shift toward the side of the pleural effusion (implying atelectasis), an underlying parenchymal or mediastinal mass, or rib erosions suggest a malignant cause. In many of these cases, flexible bronchoscopy is warranted to exclude bronchial obstruction before performing thoracoscopy or chest tube insertion.

The diagnosis of pleural carcinomatosis can be based on evaluation of the pleural fluid, pathologic evaluation of biopsied specimens, or both. Characteristically, the fluid is an exudate and is often blood-tinged. In long-standing effusions, the glucose can be low and the pH less than 7.35. The white cell count is typically low and predominantly lymphocytic. Cytologic examination can identify the primary site in up to 70% of cases. Not surprisingly, repeated thoracenteses increase the yield, as the pleural fluid malignant cell burden can increase over time, and as the malignant disease itself progresses.

Closed needle pleural biopsy yields a diagnosis in up to 50% of cases and, when combined with cytology, in close to 90%. Thoracoscopy will almost always make the diagnosis (the only false-negative findings being in patients with early malignant mesothelioma), and provide an opportunity of thoracoscopic pleurodesis in case of rapidly recurrent pleural effusions. This procedure can be performed using local or general anesthesia. It can be performed in a fully equipped endoscopy suite where patients are sedated but not intubated (recently referred to as *medical thoracoscopy*), or it can be performed in the operating room using single or double lumen endotracheal tubes and general anesthesia (*video-assisted thoracic surgery*).

The treatment and prognosis of malignant pleural disease are those of the primary tumor. Symptomatic treatment of recurrent effusions has included intrapleural instillation of sclerosing agents, such as quinacrine, *Corynebacterium parvum*, nitrogen mustard, talc, mitoxantrone, tetracycline (no longer commercially available), and pleural abrasion or pleurectomy during thoracoscopy or thoracotomy. Bleomycin has also been used but is less effective (<60% success in most studies) and far more costly. Doxycycline and minocycline are available now to replace tetracycline, but the success rates using these agents, similar to the success rate of tetracycline, are at best 72% and 86%, respectively.

Asbestos-free, sterile talc powder (also commercially available in an aerosol can) is the most effective and least expensive pleurodesis agent available. Talc pleurodesis can be achieved during thoracoscopy, at which time fluid is evacuated, talc is sprayed over all visceral and parietal pleural surfaces, and a chest tube is inserted to keep the pleural space dry and enhance complete lung expansion. Hospitalization is usually required for approximately 5 days. Talc pleurodesis can also be achieved using talc slurry (a mixture of talc powder and normal saline solution) instilled into the pleural cavity through a previously placed large-bore chest tube. The precise role for talc slurry versus thoracoscopic talc powder pleurodesis remains to be defined.

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Fifth Edition

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