Specialty Conference

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Infectious Disease Emergencies

PART III:

Patients Presenting with Respiratory Distress Syndromes

PHYLLIS OILL, MD:* The third part of this symposium is concerned with those infectious disease processes that may present with symptoms of respiratory distress (see Table III-1). Also included in this part is a discussion about anaphylaxis, since this syndrome is often seen after the administration of antibiotics and may present as respiratory distress. The infectious diseases causing respiratory distress syndromes will be divided into major symptom complexes: upper airway obstruction, hypoxia caused by pneumonia, hypoventilation syndromes and pulmonary hemorrhage.

Before the first discussant speaks about those infections that affect the upper airways and may present as upper airway obstruction (UAO) I would like to point out the importance of distinguishing UAO from involvement of the lower airways. This syndrome can indeed be a medical emergency. Clinical signs such as inspiratory stridor, grunting, pronounced retraction of the accessory respiratory muscles and prolongation of the inspiratory phase of respiration should alert a physician to the possibility of UAO. Since complete obstruction of the airway can occur at any time, patients should be examined in the sitting position with immediate availability for intubation, cricothyrotomy or tracheostomy. Undue manipulation during the physical examination may precipitate complete airway occlusion.

With the above in mind Dr. Steven Roser will discuss infections of the upper respiratory tract.

Infections of the Upper Respiratory Tract

STEVEN ROSER, DMD, MD:† *Ludwig's angina* is a rare, severe cellulitis beginning usually in the submandibular space and extending to the sublingual and submental spaces. The process is not considered a true Ludwig's angina unless all four spaces are involved. Virtually all cases result from an infected mandibular molar[1] but may also result from a penetrating injury to the floor of the mouth or from osteomyelitis of the mandible.

The first symptoms are usually related to dental pain but a rapidly developing diffuse board-

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ABBREVIATIONS USED IN TEXT

(A-a)P_{O_2} = alveolar-arterial oxygen tension difference
ADH = antidiuretic hormone
Ara-A = adenine arabinoside
Ara-C = cytosine arabinoside
ARDS = adult respiratory distress syndrome
ARF = acute respiratory failure
c-AMP = cyclic adenosine monophosphate
CHF = congestive heart failure
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
ERV = expiratory reserve volume
FI_{O_2} = fractional concentration of oxygen in inspired gas
FRC = functional residual capacity
Pa c_{O_2} = arterial partial pressure of carbon dioxide
Pa o_2 = arterial oxygen partial pressure
PEEP = positive end-expiratory pressure
$P_{\bar{V}}O_2$ = mixed venous oxygen tension
SRS-A = slowly reacting substance of anaphylaxis
TTA = transtracheal aspirate
UAO = upper airway obstruction
V_D/V_T = dead space-tidal volume ratio

like swelling on the floor of the mouth is present. There is a difficulty in eating and swallowing and patients usually have a rather high fever and a moderate leukocytosis. The disease may progress to involve the neck and be accompanied with edema of the glottis. Elevation of the tongue and edema of the glottis can lead to severe respiratory obstruction and death by suffocation. The infection may spread to the parapharyngeal space.

Most cases of Ludwig's angina are mixed infections with aerobic and anaerobic streptococci virtually always present. Fusospirochetes and other oral organisms have been isolated on various occasions.

Treatment should be directed toward localizing the infection and monitoring the patient closely for airway obstruction. Despite Ludwig's angina being a mixed infection, virtually all cases respond to high doses of parenteral penicillin. If signs of respiratory distress are observed before localization has occurred, a tracheostomy should be done. However, if localization has occurred, use of a nasoendotracheal tube will generally suffice to maintain a patent airway while the edema resolves after an incision and drainage procedure is carried out. The incision and drain-

TABLE III-1.—*Infectious Diseases Presenting as Respiratory Distress Syndromes*

Upper Airway Obstruction
- Ludwig's angina
- Parapharyngeal or retropharyngeal abscess
- Acute supraglottic laryngitis (epiglottitis)
- Acute laryngotracheobronchitis (croup)
- Diphtheria
- Anaphylaxis

Hypoxia with Severe Pneumonia
- Bacterial pneumonia
  - *Pneumococcus, Staphylococcus*
  - *Klebsiella, Pseudomonas,* other Gram-negative organisms
  - Aspiration
- Viral pneumonia, i.e. influenza
- Opportunistic infections, i.e. Pneumocystis carinii
- Fungal infections
- Tuberculosis
- Infective endocarditis (right sided)*

Pulmonary Hemorrhage
- Lung abscess
- Tuberculosis
- Fungal infections

Hypoventilation Syndromes
- Guillain-Barré
- Poliomyelitis
- Rabies
- Tetanus
- Botulism
- Tick paralysis
- Diphtheria
- Neuromuscular blockade associated with antibiotic administration

*Discussed in Infectious Disease Emergencies, Part II: Patients Presenting with Cardiac Decompensation and Circulatory Insufficiency (Shock).

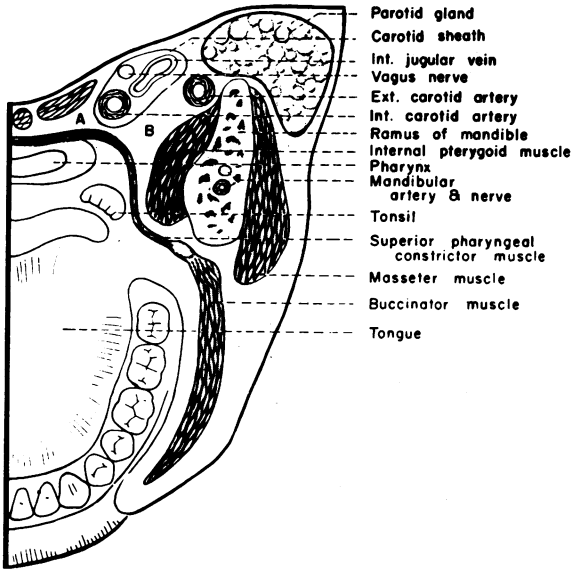

Figure III-1.—Horizonal section through the head at the level of the mandibular occlusal plane. The parapharyngeal spaces are indicated: **A**, retropharyngeal space, **B**, lateral pharyngeal space. (Reproduced by permission from: Shafer WG, Hine MK, Levy BM: A Textbook of Oral Pathology, 3rd Ed. Philadelphia, W B Saunders, 1974, p 463.)

age should be done in both the submandibular and submental areas and care taken to drain above the mylohyoid muscle.

Parapharyngeal Abscess

The lateral pharyngeal space is bounded anteriorly by the buccopharyngeal aponeurosis, the parotid gland and the pterygoid muscles; posteriorly by the prevertebral fascia; laterally by the carotid sheath, and medially by the lateral wall of the pharynx (see Figure III-1). Infection of the space may be by way of vascular or lymph channels from the tonsils, pharynx, nose, sinuses, adenoids, lymph nodes, mastoid or petrous bone. It usually begins as a cellulitis involving the anterior portion of the space with an abscess forming later in most of the cases. Infection may spread to the posterior part of the space which contains the carotid sheath. Thrombosis of the jugular vein, erosion of the carotid artery leading to fatal hemorrhage and mediastinitis are potential complications resulting from infections in the area.

A patient will usually note symptoms four to seven days after the infection has begun. Pain, usually referred to the ears, dysphagia and trismus are the most prominent symptoms. On examination of the oral cavity, displacement of the lateral pharyngeal wall without swelling of the tonsil is seen, which helps differentiate infections in the lateral pharyngeal space from a peritonsillar abscess. Fever, adenitis and leukocytosis are usually present. A lateral radiograph of the neck can aid in diagnosis when it shows displacement of the trachea anteriorly.

The bacteria involved are usually hemolytic and nonhemolytic streptococci; fusiform bacilli, pneumococci and staphylococci have also been implicated.

Therefore, high dose penicillin is the drug of choice. Bed rest and hot moist rinses are important adjunctive measures before localization. Once localization has occurred drainage of the abscess is necessary. This may be done through an intraoral or extraoral approach. Without appropriate drainage respiratory distress can occur from either mechanical obstruction or strangulation from sudden rupture of the abscess, especially in the young.

Retropharyngeal Abscess

The retropharyngeal space is bounded anteriorly by the wall of the pharynx, posteriorly by the prevertebral fascia and laterally by the lateral pharyngeal space and carotid sheath (see Figure III-1). It extends from the base of the skull along the prevertebral space to the posterior mediastinum. However, the attachment of the superior constrictor at the second cervical spine usually confines the abscess above it. An abscess in this area is uncommon. Factors leading to infection of this space are suppurative nodes, injuries and foreign bodies to the posterior pharyngeal wall and extension from infections of the parapharyngeal space. The bacteria involved are the same as those implicated in parapharyngeal abscesses.

A patient is usually first made aware of an infection in this area by painful swallowing. If the swelling is large enough, choking respiration or even dyspnea can occur. Cervical adenitis, cough, fever and leukocytosis are present. On examination of the oral cavity a smooth bulging mass will be seen displacing the buccopharyngeal fascia forward impinging on the pharynx. A lateral radiograph of the neck will show an anterior bulging of the posterior pharyngeal wall.

The danger of a retropharyngeal abscess in very young patients is chiefly due to suffocation and strangulation upon spontaneous rupture of the abscess. Older patients can usually manage the sudden drainage of pus because of better pharyngeal and cough reflexes. Other complications can include spread to the posterior mediastinum, meningitis, hemorrhage secondary to erosion into vessels, pressure on the epiglottis and larynx secondary to edema and aspiration of infected material.

Most of these cases can be treated with antibiotics, only if therapy is commenced early. Delay in treatment results in suppuration with fluctuation. When this occurs surgical intervention is mandatory. Obstruction of the airway demands immediate drainage. Precautions must be taken to prevent aspiration when draining these abscesses. Occasionally the edema and inflammation will lead to respiratory embarrassment before localization. In these cases a tracheostomy is best carried out early.

Acute Supraglottic Laryngitis or Epiglottitis

Acute supraglottic laryngitis or epiglottitis is a potentially lethal disease in children. It occurs not uncommonly in adults.

The pathophysiology involves a severe cellulitis of the tissues of the epiglottis and aryepiglottic folds. Because of the relatively small size of the

supraglottic larynx in children, small amounts of swelling predispose to obstruction. Thick inspissated secretions complicate the obstruction from edema. Hemophilus influenzae type B has been the bacteria cultured most consistently,[2] although infrequently other bacteria such as Staphylococcus aureus and hemolytic streptococcus have been isolated.

The course of the disease is usually rapid, progressing from mild upper respiratory tract infection type symptoms to almost complete respiratory obstruction over a period of 6 to 12 hours.[3,4] The disease usually begins with fever and malaise, with dysphagia as an important early symptom. The patients tend to remain quiet, concentrating on breathing. A typical presentation is a child sitting, leaning forward with an open mouth and tongue protruding to facilitate breathing. Compared with croup, the respirations are quiet because any increase in the effort to breath results in the edematous epiglottis acting like a ball valve which will completely obstruct the larynx on each inspiratory effort. As the edema progresses, soft tissue retraction, restlessness and cyanosis appear. If treatment does not intervene, respiratory arrest will occur.

On examination of the oral cavity the oropharynx will be seen to be somewhat injected with pooling of secretions. With depression of the tongue, a cherry red, edematous epiglottis can be seen projecting over the posterior tongue. Extreme caution must be exercised while carrying out this maneuver since this examination alone can result in complete obstruction. Direct laryngoscopy is contraindicated unless personnel and equipment are available for emergency intubation or tracheostomy since the procedure can also easily precipitate obstruction.

If visualization of the epiglottis for confirmation of epiglottitis cannot be accomplished, a lateral radiograph of the neck may show there to be characteristic supraglottic swelling. A radiograph of the chest is always indicated because atelectasis and pneumonitis may accompany this disease.

These patients must be admitted to hospital immediately and placed in an intensive care unit with appropriate equipment for airway maintenance by the bedside. Since it is always impossible to predict in which patients complete airway obstruction will develop, and since the morbidity and mortality rate is significant, many authors feel a tracheostomy is completely justified as a routine procedure.[4,5] A tracheostomy should be done in any case where there is any degree of obstruction or whenever experienced personnel are not available for observation. An alternative method of providing an airway, which requires experience, is prolonged nasotracheal intubation.[6] If respiratory obstruction is not one of the presenting signs, vigorous conservative therapy may obviate having to establish an airway. While being observed, if any respiratory symptoms or obstruction occur, an endotracheal tube should be inserted immediately followed by a tracheostomy done under more orderly circumstances.

Conservative treatment includes use of parenteral fluids, humidity, oxygen and mucolytic agents. Patients should be kept quiet to prevent anxiety. Antibiotics should be instituted. Administration of ampicillin, 150 to 200 mg per kg of body weight per day, is standard therapy. Chloramphenicol is an acceptable alternative if a patient is allergic to penicillin. Steroids may be of value in limiting progression of the inflammation and edema.

Acute Laryngotracheobronchitis or Croup

Acute laryngotracheobronchitis, or croup, is a severe acute inflammatory disease of the larynx, trachea and bronchi usually involving children under five years of age. The most critical feature of this disease is the edematous swelling of the conus elasticus with narrowing of the infraglottic area (see Figure III-2). An intense inflammatory

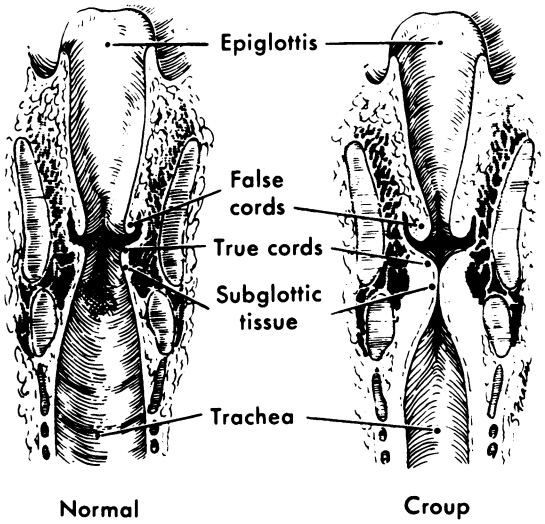

Figure III-2.—Schematic diagram of larynx and trachea in viral croup as compared with normal appearance. (Reproduced by permission from: Krugman S, Ward R: Infectious Diseases of Children and Adults, 5th Ed. St. Louis, C V Mosby, 1973, p 208.)

reaction of the mucosa with loss of epithelium and an outpouring of thick secretions accompanies the swelling. Therefore, obstruction results from both secretional and mechanical factors. The infectious agents are predominantly the respiratory viruses, parainfluenza type 1, 2, 3 and influenza A_2 and B.[7] Secondary infection with Gram-positive bacteria may occur.

The disease usually begins as a mild upper respiratory tract infection. This is followed by a croupy, barking, nonproductive cough. The onset of the cough is usually at night. The course may be either self-limiting or progress to respiratory obstruction. Although the onset and progression is gradual, occasionally sudden deterioration occurs. Respiratory difficulty is characterized by chest wall retraction, prolonged inspiratory phase and expiratory wheezing. Also, malaise, tachycardia, fever and restlessness are usually present.

The diagnosis is based on clinical presentation and findings of physical examination. On examination of a child with this disease, nasal discharge is noted, and infected pharynx with normal appearing epiglottis, tachypnea and inspiratory stridor. A lateral radiograph of the neck can be useful by showing the characteristic infraglottic narrowing.

Management is similar to that in supraglottic laryngitis—which includes humidification, hydration, oxygen and antibiotic therapy. Use of sedatives, which may mask signs of respiratory failure, and narcotics, which suppress the cough reflex, is to be avoided. The child should be spared all needless procedures. The use of steroids is debatable with some authors suggesting that they are ineffective and enhance susceptibility to infection,[8,9] and others finding that if steroids are given in adequate doses this may shorten the length of the disease and the stay in hospital.[10,11] At present the routine use of steroids in the disease is not justified. The final decision will rest with the responsible physician, who must weigh the relative merits and risks of therapy for a particular patient.

Although the cause of this disease is viral, when the patient is febrile with a leukocytosis, use of antibiotics should be considered.[12] Ampicillin, 150 to 200 mg per kg of body weight per day, is the drug of choice.

As in epiglottitis, vigorous conservative therapy will usually be sufficient in most of the early cases. However, any sign of respiratory obstruction such as increased respiratory rate, retractions, restlessness, tachycardia and cyanosis will make a tracheostomy necessary. This is necessary in approximately 7 percent of all cases.[13]

Diphtheria

Diphtheria is now an uncommon acute infective process involving all or part of the upper respiratory tract. It occurs in children over six years of age. The pathophysiology involves a superficial infection involving the mucous membranes. Epithelial necrosis is accompanied by an outpouring of serum and this agglutinates into a firmly attached membrane. The bacteria elaborates an exotoxin which produces more necrosis. This exotoxin when absorbed systemically attacks heart muscle and peripheral nerves. Death may result from airway obstruction or heart failure.[14]

The disease is caused by Corynebacterium diphtheriae, a Gram-positive organism of which there are three types. The gravis type is responsible for diseases in North America. The usual spread is by droplet, but this organism can change from a nonvirulent strain to a toxin producing virulent form which probably accounts for isolated cases.[15] Immunization has kept this disease to a minimum.

The incubation period is from one to six days. The onset is characterized by a slight sore throat, malaise and low grade fever. On examination of the oral space the presence of a grayish white membrane on the tonsils, pharyngeal wall or larynx will be noted. Cough, hoarseness, stridor and progressive signs of respiratory obstruction can occur. This is related to both edema and the membrane. Sudden asphyxia can occur when a piece of the membrane dislodges and becomes entrapped in the larynx. Cervical adenitis is usually present and, if pronounced, gives a characteristic bull neck appearance.

Diphtheria must be considered in the differential diagnosis of any membranous pharyngitis or laryngitis. If microscopic examination of a piece of the membrane shows the organism, that makes the diagnosis.

Treatment includes administration of antitoxin, penicillin and oxygen, and continuous monitoring of the patient's respiratory status. If symptoms of respiratory obstruction are pronounced, a tracheostomy is indicated. Bronchoscopy should be done first so that any membrane in the trachea or bronchi may be removed as well as to provide an airway during the tracheostomy.

DR. OILL: A further discussion of the effects of diphtheria exotoxin will be presented later in this session under the topic of hypoventilatory syndromes. In addition, more extensive reviews of oral pathology and infectious diseases of children have been published.[16,17]

The next area of consideration will be those intrathoracic processes which often manifest as respiratory distress associated with hypoxia. Dr. Jeffrey Galpin will discuss the varied causes of infective pneumonitis and Dr. Irwin Ziment will then speak about the physiology and management of severe pneumonia.

Infectious Pneumonias

JEFFREY GALPIN, MD:* Pathologists may describe pneumonia in terms of "interstitial," "alveolar" or "acute necrotizing" processes, while radiologists focus on anatomical terminologies of "lobar," "peribronchial" or "cavitary." Finally, clinicians may direct their assessment of pneumonia in the context of "overwhelming," "atypical" or "opportunistic." However, far more useful is an effort to describe infectious pneumonia as due to a specific etiologic agent with directed, specific therapeutic modalities.

When a person presents to an emergency department with respiratory distress several factors must be considered. Epidemiological factors like age, setting of the infection and the season of the year can be helpful (see Table III-2). Clinical findings such as underlying diseases, duration and severity of illness, and particular signs and symptoms also may aid in diagnosis. Finally, the radiologic characteristics, peripheral leukocyte count and description of sputa and transtracheal or thoracic aspirate greatly assist in allowing an intelligent approach toward treatment.

Pneumococcal Pneumonia

In a middle-aged or elderly person in whom pharyngitis, chills, fever and pleuritic pain have occurred for several days associated with dyspnea, tachypnea and productive bloody or greenish mucopurulent sputum, one must seriously consider a diagnosis of pneumococcal pneumia, now known as Streptococcus pneumonia. This organism accounts for a minimum of 80 percent of the

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TABLE III-2.—*Key Associations of Pneumonia*

Organism	*Age*	*Leukocyte Count*	*Specific Underlying Disease*	*Other Complications*
Pneumococcus	Severe in old	N↓↑	Hemoglobinopathies, multiple myeloma, CHF, alcohol, diabetes mellitus	Endocarditis, meningitis, arthritis
Staphylococcus	Old	↑	COPD, CHF, drug abuse, viral pneumonia, diabetes mellitus, granulocytopenia, cystic fibrosis	Meningitis, endocarditis, abscess
Klebsiella	Old	↑	COPD, aspiration, drug abuse, CHF, diabetes mellitus, hospital-acquired infections	Chronic pneumonia, abscess, sepsis
Pseudomonas	..	↑↓	Aspiration, hospital-acquired infections, drug abuse, granulocytopenia	Multiple abscesses, sepsis
Influenza	..	N↑↓	COPD, CHF, mitral valve disease, pregnancy	Secondary bacterial pneumonia, encephalitis, myocarditis
Pneumocystis carinii .	..	N	Lymphoproliferative diseases with immunosuppressive therapy	.....
Herpes viruses	Very young	N	Lymphoproliferative diseases and other neoplasms, diseases where cytotoxic drugs and steroids used	Dissemination to all organ systems
Anaerobes	..	↑	Aspiration, alcohol, seizures, dysphagia, altered state of consciousness	Endocarditis, abscesses, empyema, sepsis
Mycoplasma	Young	N↑↓	.....	Neurologic, gastrointestinal, dermatologic
Psittacosis	..	N↑↓	.....	Encephalitis
Q Fever	..	N↑↓	.....	Hepatitis, endocarditis
Coccidioidomycosis ..	..	N↑↓	Immunosuppression	Meningitis, bone, other metastatic sites
Tuberculosis	..	N↑↓	Immunosuppression, bacterial pneumonias	Miliary or distant infection in almost any organ
Nocardia	..	↑↓	Immunosuppression	.....

COPD = chronic obstructive pulmonary disease CHF = congestive heart failure N = normal

bacterial pneumonias seen.[18] Herpes labialis, an ileus or splinting of the chest due to pleurisy, may be associated with this pneumonia. Signs of lobar consolidation are found on physical examination, and fine crackling rales and pleural friction rub are common. The patient's temperature may range from 102 to 106°F and febrile peaks often occur in the late afternoon.

On a Gram stain of the sputum, many polymorphonuclear leukocytes and Gram-positive encapsulated, lancet-shaped diplococci singly or in short chains are seen. More than 30 organisms seen in a single high-power microscopic field correlate with high counts from smears of the lung at autopsy and therefore a poorer prognosis. A web-like appearance on Gram stain suggests the presence of large amounts of soluble specific capsular substance which frequently is indicative of type III organisms.[18] When sputum is not expectorated or oropharyngeal infection obscures the diagnosis, then a transtracheal aspirate (TTA) study is required.

Leukocyte counts range to 40,000 per cu mm and there is usually a shift to the left. A normal leukocyte count or leukopenia often occurs in the fulminant or bacteremic infection. Jaundice occurs not infrequently, being due to hemolysis from pneumolysin within the lung and liver.[18]

Radiologically, a classic lobar pneumonia is seen especially in one lower lobe although multiple lobes may be involved. Cavitation, empyema and effusion occur but are uncommon.

Certainly alcoholism, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes mellitus, SS and SC hemoglobinopathies increase the morbidity and mortality of pneumococcal pneumonia. Patients with bronchogenic carcinoma, multiple myeloma, asplenism and hypogammaglobulinemias are also predisposed to this illness. Treatment with 600,000 units of penicillin G given intravenously every six hours is the therapy of choice. Other effective agents in this disease are the cephalosporins, clindamycin and erythromycin. Mortality and bacteremia increase with age.[19] Bacteremias may result in septic arthritis, meningitis, endocarditis, empyemas of the gallbladder, peritonitis and disseminated intravascular coagulation. Pneumococci are delicate organisms and the culture media should be used directly at the bedside. Carbon dioxide is required by many types of pneumococci and immediate incubation is necessary. Even without a bacteremia pneumococcal antigen can be detected rapidly in serum by the use of immunoelectrophoresis and polyvalent antipneumococcal serum.

Staphylococcal Pneumonia

Staphylococcus aureus represents about 1 percent of all pneumonias and occurs sporadically except during influenza or measles epidemics.[20] With leukemia, collagen vascular disease or heroin or alcohol abuse there is greater susceptibility to this disease.

Multiple chills, high fever, dyspnea, cough and pleurisy occur early in the disease. Creamy sputa containing clusters of large Gram-positive cocci are characteristic. Most patients are very ill and vascular collapse is frequently seen.

Leukocytosis is frequently seen in these patients, although bacteremia may be uncommon. Blood cultures, however, must be obtained as in all suspected bacterial pneumonias. If a staphylococcal bacteremia does exist, the possibility of endocarditis or other metastatic complication must be strongly considered.[21]

The characteristic findings on radiologic examination include a patchy central or lower lobe infiltrate which may progress to abscess, empyema or pyopneumothorax. Signs of frank consolidation are rare while radiologic evidence of a pneumatocele are common.[18,22] Penicillin G, 1.5 million units, and methicillin, 1.5 grams, given intravenously every four fours should be administered until antibiotic sensitivity data are available. Patients allergic to penicillin should be given vancomycin, 2 grams administered intravenously in four divided doses every 24 hours, or cephalothin, 1.5 grams administered intravenously every four hours.

Patients presenting with staphylococcal pneumonia and bacteremia may also have associated cutaneous lesions such as subcutaneous abscesses, petechiae, Osler's nodes, urticaria, erythema multiforme or infected bullous eruptions. Other clues to the diagnosis may be a purulent otitis media, subcutaneous emphysema or suppurative parotitis.[23]

Klebsiella Pneumonia

Klebsiella is an organism usually acquired as a superinfection. Klebsiella occurs as normal oropharyngeal flora in 1 to 25 percent of people. Aspiration, especially related to ventilatory equipment or associated with the debilitated host, is a common predisposing factor in this illness.[24] This

organism invades the lungs after a preceding viral disease or in association with other pulmonary parenchymal disease. Chills, hectic fever, pleurisy, dyspnea and occasionally jaundice and emesis—especially in patients with predisposing illnesses such as alcoholism, diabetes, CHF, COPD and renal or neoplastic disease—must alert one to a possible Klebsiella pneumonia (see Table III-2). Clinical evidence of Gram-negative sepsis is not uncommon.

Profound prostration and sustained spiking irregular fevers are usually seen with this pneumonia. Physical findings are those of lobar consolidation with or without abscess. There is an acute loss of lung volume resulting from the necrotizing effects of this pneumonia. Therefore, the involved hemithorax may show an elevated diaphragm and ipsilateral tracheal shift.[25]

On studies of sputum many polymorphonuclear leukocytes and many Gram negative encapsulated rods are noted. Leukocytosis is frequent but a third of patients have leukopenia. Positive blood cultures may be present, and along with leukopenia, portend a worse prognosis.

On x-ray examination lobar consolidation is seen, or occasionally bronchopneumonia especially of the upper lobe. Bulging interlobar fissures and sharp borders of the infiltrate are characteristic. Multilobe involvement and abscesses occur in about 50 percent of patients.

Treatment involves using an effective aminoglycoside such as gentamicin, given intravenously at a dosage of 1.7 mg per kg of body weight every eight hours (providing renal function is normal) for at least 10 to 14 days or until parenchymal clearing occurs.

Chronic Klebsiella pneumonia is a distinct syndrome with patients presenting with several weeks of malaise, cough and occasional hemoptysis. X-ray studies show bronchopneumonia, bronchiectasis or radiological evidence of thin walled pulmonary cavities. The diagnosis is established by isolation of the organism from pulmonary secretions (most reliably by study of TTA as opposed to expectorated sputum). Long-term antibiotic therapy is frequently necessary for effective eradication of the infection. Not uncommonly surgical resection of the infected lung may be required if medical therapy alone is ineffective.

Pseudomonas Pneumonia

Pseudomonas pneumonia, like Klebsiella infection, occurs in a similar milieu—that is, secondary to aspiration, in superinfection, in burn patients, in immunosuppressed persons or in chronically ill patients. Patients present with dyspnea, fever and signs of infiltrative lung disease. On radiologic examination characteristically a necrotizing pneumonia with microabscess formation is shown. Studies of sputa show Gram negative rods. If bacteremia occurs, the prognosis is very bleak with a mortality of almost 100 percent.[26] Persons with leukopenia are particularly predisposed to Pseudomonas infections including pneumonia and bacteremia.[27]

Aminoglycosides with antipseudomonas activity, such as gentamicin, tobramycin or BB-K8 (Amikacin®), are the drugs of choice. Despite this therapy, the mortality is 25 to 60 percent.[28] Carbenicillin (30 to 40 grams per day) should be added to the regimen with pronounced leukopenia, presence of bacteremia, extensive pulmonary involvement or failure to respond to an aminoglycoside alone.

Influenza Pneumonia

Pneumonia due to influenza virus is generally seasonal and can reach epidemic magnitude. Since the pandemic in 1918 and 1919 there have been regular epidemics. The pandemic of 1957 to 1958 marked the appearance of the H2/N2 antigen subtype which resulted in more than 86,000 deaths in the United States. Since 1889 in the United States there have been 52 epidemics or pandemics.[29] Outbreaks are characterized by abrupt onset with a high incidence of rapid but irregular spread through communities. The peak is reached and passed in about one month.

A patient seen in the emergency department may complain of the onset of fever and chilliness, with episodes of sweating, headache and myalgias. Minor upper respiratory symptoms may precede the constitutional complaints. A nonproductive, painful cough and prostration are characteristic. Conjunctival irritation and minor nasal obstruction are frequent. Abdominal pain and diarrhea are rare.

Gram stain of the sputa is nondiagnostic and findings on radiological examination include a wide spectrum from normal lung fields to bronchopneumonic infiltrates progressing to true lobar consolidation. Neutrophilia may be seen initially, but usually leukopenia with a relative lymphocytosis is seen. In up to 75 percent of uncomplicated cases electrocardiographic changes of T wave inversion or depression are seen.

Persons with cardiopulmonary disease (such as COPD or rheumatic heart disease), pregnant women, and elderly and debilitated patients are predisposed to complication of this illness. These patients do poorly with primary influenza pneumonia and also secondary staphylococcal, pneumococcal or Hemophilus influenzae infections often develop. These susceptible persons are also more likely candidates for influenzal encephalitis, radiculitis, seizures, myocarditis with CHF or arrhythmias and primary hemorrhagic pneumonitis. These patients in whom secondary complications do develop are often quite ill when they seek medical care. Hypoxia is frequently pronounced and it is often difficult to determine if a superimposed bacterial infection exists. It is in these patients that a TTA study is indicated. Treatment with appropriate antibiotics should be carried out if bacteria are seen on Gram stain of the aspirate or cultures yield a pathogen. Amantadine hydrochloride is active against influenza type A primarily on a prophylactic basis; however, recent evidence indicates that the drug also possesses moderate therapeutic effects during the active infection.[30] Unfortunately, there is no completely adequate therapy for the viral pneumonia but certainly secondary infection and other complications must be anticipated and treated appropriately.

Pneumonias in the Altered Host

The discussion to this point has emphasized particular infective agents that comprise most types of pneumonia seen in patients presenting to an emergency department. The diagnosis and treatment of other types of pneumonia will now be approached in terms of certain underlying diseases and specific alterations in host defenses.

Aspiration Pneumonia and Lung Abscess

Aspiration must be suspected as the pathogenesis of pneumonia in a person brought to an emergency department with a history or findings of an altered state of consciousness and pulmonary infiltrate. Alcoholism, heroin addiction, cerebrovascular accidents, seizures, cardiogenic shock and encephalitis are typical examples. Additionally, abnormalities in swallowing or cough reflex predispose to aspiration. More than half of the patients with aspiration pneumonia will present with infiltrates in the dependent lobe of the lung reflecting a positional or gravitational pneumonia. About 20 percent of the patients will present with a necrotizing pneumonia defined as a suppurative infection characterized by multiple small cavities usually within a single pulmonary lobe. A third of patients expectorate putrid sputum and most present with an elevated leukocyte count and fever. Finally, the cause of lung abscess in about a third of patients with this disease is secondary to an episode of aspiration.[31,32]

The organisms involved are those normally found in the mouth. Therefore, the infection is usually polymicrobial and includes aerobic Staphylococcus aureus, Group A Beta hemolytic streptococci, Streptococcus pneumoniae, Klebsiella, Escherichia coli, Pseudomonas aeruginosa, Proteus species and anaerobic organisms like Bacteroides melaninogenicus, Bacteroides oralis, streptococci, Fusobacterium nucleatum, Clostridium and possibly Bacteroides fragilis.[33] Because the organisms are derived from the normal flora of the oropharynx, a sputum culture is of little value. Meaningful bacteriological data can only be obtained by examining secretions from the lower respiratory tract either by TTA study or transthoracic needle aspiration. Additionally, examination of pleural fluid (if present) is a reliable source for microbiological information. A mixed anaerobic and aerobic infection is found in most patients with aspiration pneumonias. Uncomplicated aspiration pneumonia occurring outside a hospital will usually respond effectively to parenteral penicillin in doses of 2 to 4 million units a day. Clindamycin, 600 mg given intravenously every eight hours, is an acceptable alternative. Aspiration occurring in hospital will generally necessitate additional therapy for aerobic Gram-negative rods (such as use of gentamicin) until cultural data become available or if the patient's condition deteriorates on single antibiotic therapy. The role of Bacteroides fragilis is unclear in aspiration pneumonia. If the organism is isolated from blood specimens or repetitively from respiratory secretions, therapy should include agents effective against these bacteria (such as clindamycin or chloramphenicol).

Primary lung abscess may develop secondary to aspiration. The most frequent sites for this lesion are identical to those of aspiration pneumonias and include the posterior segments of the upper lobes or superior segments of the lower lobes, or the basilar segments of the lower lobes. Common symptoms include cough with putrid sputum production, pleuritic chest pain and

hemoptysis. Weeks of fever, malaise, anemia and weight loss are also reported.[34,35]

Most evidence points to a polymicrobial flora with anaerobes predominating within the lung abscess. These include Fusobacterium nucleatum, Bacteroides melaninogenicus, Peptostreptococcus, Peptococcus and Eubacteria.[33] Chemotherapy should be with either parenterally given penicillin G, 4 to 8 million units a day, or clindamycin 600 mg given intravenously every 6 to 8 hours. Several weeks to months of chemotherapy and good pulmonary drainage may be required until findings on studies of sputa return to normal and the cavity has resolved to a significant degree. Rarely, surgical resection is required after failure of medical therapy. The size of the cavity and duration of symptoms before therapy are important prognostic factors.

Necrotizing pneumonias as well as lung abscess may occur secondary to E. coli, Proteus species and Serratia, and less commonly with organisms such as Nocardia,[36] Actinomyces, Aspergillus[37] and Mycobacteria tuberculosis. Moreover, other disease processes like bronchogenic carcinoma, right-sided endocarditis and septic emboli from other sources may produce similar clinical features. A patient may present with hemoptysis or frank pulmonary hemorrhage secondary to the necrotizing process.

Finally, an acute empyema may result from extension of a necrotizing pneumonia, abscess or, in granulomatous disease, from a mediastinal lymph node. Findings here are identical to those in lung abscess and include intermittent fever, sweating, chest pain, anemia, leukocytosis and weight loss. Treatment includes use of appropriate antimicrobial agents, provision of adequate drainage and obliteration of the dead space.

Pneumonia in Immunosuppressed Patients

Pneumocystis carinii pneumonia should be considered in immunosuppressed patients in whom an insidious onset of progressive dyspnea and nonproductive cough develops, frequently without pulmonary auscultatory abnormalities.[38,39] Hypoxia is seen especially in later stages of this disease. Fever is not necessarily a component. Classic radiologic evidence of a pneumonia need not be present but in progressive cases bilateral interstitial features are frequently seen in the lower lobes. Definitive diagnosis is made by identification of the pathogen histologically by silver methenamine stain on lung tissue obtained by biopsy, by pulmonary lavage or occasionally by bronchial brushings. The diagnosis should be confirmed as soon as possible, and if a high index of suspicion exists therapy with pentamidine isethionate (4 mg per kg of body weight per day given intramuscularly) should be carried out. Administration of pyrimethamine and sulfadiazine is an alternative therapeutic regimen. Pneumocystis carinii may be found associated with other infections like the cytomegalovirus.

In any immunosuppressed patient presenting with bronchopneumonia a localized or disseminated cytomegalovirus or herpes infection may be present. Viral cultures of sputa, TTA studies, buffy coat of the blood and tests of urine and stool specimens should be done. Urine sediment can be examined for inclusion bodies to aid in the diagnosis. Other signs of dissemination such as neurologic or gastrointestinal disturbances should be carefully sought. If these viral infections are strongly considered, then immunosuppressive drugs should be discontinued or tapered if possible. The efficacy of adenine arabinoside (Ara-A) and cytosine arabinoside (Ara-C) in the treatment of these viral infections has not been clearly delineated.

Additionally, in an immunosuppressed patient, other opportunistic agents must be considered as a potential cause of pneumonia. Infectious granulomatous disease (such as tuberculous or fungal), Nocardia, Actinomyces, Gram-negative bacilli, or even Toxoplasma are agents that fall into this category.

General Comments

Certain underlying diseases may suggest specific infective pneumonias. For example, the presence of multiple myeloma in a patient should make one suspicious of pneumococcal pneumonia and less commonly Gram-negative pneumonias, unless immunosuppressive therapy is being carried out. Patients with sickle cell disease are also predisposed to pneumococcal pneumonia. In persons with lymphoma and pneumonia studies must be done for common pathogens—but also for organisms such as cytomegalovirus, herpes simplex and zoster,[40,41] Toxoplasma[42] and Aspergillus, as well as Mycobacteria. Additionally, in a patient receiving high dose steroids there is an increased risk of a herpes virus, toxoplasma, Pneumocytis carinii or fungal pneumonia developing.

Bacterial endocarditis should be suspected in patients in whom there is evidence of multiseg-

mental bronchopneumonia or necrotizing pneumonia. More than half of the persons with right-sided endocarditis present as having multisegmental pneumonia and often no cardiac murmur may be present. Furthermore, in persons with septic or suppurative thrombophlebitis frequently there are signs of septic emboli to the lung. In many of these patients, other evidence of endocarditis may be present, such as hematuria, cutaneous or conjunctival petechiae or metastatic abscesses.

Bronchopneumonia in a young person is most frequently due to pneumococcal, mycoplasmal or adenoviral infections.

Unusual associations—such as exposure to specific animals—should bring to mind such pneumonic entities as psittacosis or Q fever. Geographic settings may make it more likely to include histoplasmosis or coccidioidomycosis in the differential diagnosis. Finally, personal contacts may suggest diseases such as tuberculosis, and social habits such as heroin addiction or alcoholism may suggest their own list of infective pneumonias and complications.

Although the diagnosis of a specific infective pneumonia is difficult, especially in an emergency situation, a logical approach, utilizing a knowledge of the above diseases combined with a good history, physical examination and limited laboratory evaluation, is possible (see Table III-3).

The Physiology and Management of Severe Pneumonia

IRWIN ZIMENT, MD:* Most infectious diseases that affect the lungs result in difficulties in oxygen transportation through the airways, and thereby cause hypoxemia. Bacterial infections lead to consolidation, and the resultant alveolar filling places a barrier between the gas in the airways and the blood in the alveolar capillaries. Many other infections, particularly those caused by respiratory viruses, result in interstitial inflammation; if this is not extensive, then there is relatively little total impedance to gaseous exchange. However, many interstitial infections involve the whole lung, and the generalized process leads to pronounced hypoxemia, which rapidly worsens as the inflammatory process spreads into the airways and alveoli.

Pneumonic infections may be localized, causing lobar consolidation, or more generalized, resulting in multilobar pneumonia or bronchopneumonia. The infecting organism may result primarily in an alveolar or an interstitial reaction, but in severe cases there is a mixed pattern. An extensive multilobar infection tends to produce a proportionally severe physiologic derangement, whatever the particular infecting agent may be. If a patient has abnormal lungs to begin with or if secondary cardiopulmonary complications develop, death from hypoxemia may supersede. Severe pneumonia is characterized by toxemia and hypoxemia, and the underlying abnormalities in the lung consist of interstitial inflammation with edema, capillary damage and airway occlusion by a conglomeration of mucus, organisms, inflammatory cells, blood and serum.

The major problem in overwhelming pneumonia is hypoxemia; numerous individual factors contribute to this abnormality.[43] Apart from the increased separation between airway gas and capillary blood caused by infected mucus and bronchioalveolar secretions, the mechanics of breathing and the distribution of blood flow are adversely altered. The fever, toxemia and increased metabolic demands result in additional tissue demands for oxygen, while pleural pain and the increased stiffness (that is, decreased compliance) of the lungs result in additional work because of the inefficient, rapid, shallow breathing, which further increases oxygen needs. In the lungs, the inflammatory reaction results in rela-

TABLE III-3.—*Diagnosis of Pneumonia by Location and Form*

Location:	
Lobar consolidation	Diplococcus
Bulging right upper lobe fissure	Klebsiella
Patchy central infiltrates	Staphylococcus or viral
Patchy bronchial infiltrates	Mycoplasma
	Influenza
	Q fever
	Psittacosis
Form:	
Granulomas or multiple nodules	Tuberculosis
	Histoplasmosis
	Coccidioidomycosis
	Klebsiella
Abscess	Anaerobes, aspiration
	Gram-negative rods
Empyema	Anaerobes
	Staphylococcus
	Gram-negative rods
Necrotizing pneumonias	Anaerobes, aspiration
	Gram-negative rods
	Nocardia
Microabscesses	Pseudomonas

*Associate Chief, Department of Medicine, UCLA San Fernando Valley Medical Program; Chief of Medicine, Olive View Medical Center; Associate Professor of Medicine, UCLA School of Medicine.

tive vasodilation in the involved areas where gaseous exchange is poor: the increased blood flow to poorly ventilated zones constitutes a right-to-left shunt, with a further increase in systemic hypoxemia. Further circulatory derangement will occur with toxic capillary damage, localized thrombosis, disseminated intravascular coagulation, heart failure or adverse fluid balance; the existence of all these complications characterizes the severe respiratory insufficiency of the so-called adult respiratory distress syndrome (ARDS) or acute respiratory failure (ARF) which might occur in overwhelming pneumonia. This condition is similar to the posttraumatic respiratory syndrome, which has been the subject of intensive study; some of the following discussion is based on the work of surgical researchers.[44]

Physiologic Findings in ARDS (Table III-4)

Patients with severe pneumonia are not in a condition to permit routine pulmonary function testing, but many abnormalities in function can be determined at the bedside or can be deduced from clinical and radiologic findings. Usually, studies of the arterial blood gases provide the most critical information, and practical clinical management is largely dependent on serial blood gas evaluation.

Blood Gases. When evaluating a blood gas result in an individual patient, one must take into consideration various factors such as the ambient atmosphere and pressure, and the position and age of the patient. For example, the normal findings in a healthy 20-year-old person standing up in Los Angeles differ notably from those in a relatively intact 80-year-old person lying down half way up Mount Whitney. In Los Angeles, an arterial oxygen partial pressure ($Pa\,O_2$) of less than 60 mm of mercury is probably abnormal; certainly a $Pa\,O_2$ less than 40 mm of mercury is indicative of a severe problem, which generally demands active alleviation. A hypoxic patient usually attempts to improve oxygenation by hyperventilating, thus causing a fall in the arterial partial pressure of carbon dioxide ($Pa\,CO_2$); if the $Pa\,CO_2$ increases, this indicates that severe respiratory insufficiency has developed. However, it is difficult to say which of the following patients is in the worse condition: Patient A with a $Pa\,O_2$ of 60 and a $Pa\,CO_2$ of 55, or Patient B with a $Pa\,O_2$ of 55 and a $Pa\,CO_2$ of 40 mm of mercury. Patient A may be in greater danger of hypoventilatory respiratory failure, such as often occurs in a patient with chronic airway disease in whom pneumonia develops and who gradually becomes exhausted, until apnea eventually occurs. However, Patient B who has more severe lung disease, with greater hypoxemia, nevertheless may have more staying power, with less danger of hypoventilatory respiratory arrest. Clinical judgment, rather than blood gas study results, is required when a prognosis is offered for such patients.

In practice, it is useful to consider two values in the assessment of a patient with ARDS. The first is the alveolar-arterial oxygen tension difference, (A-a) P_{O_2}, which is approximately equal to $140-(Pa\,O_2+Pa\,CO_2)$. For Patient A the (A-a) $P_{O_2}=140-(60+55)=25$, whereas for Patient B, (A-a) $P_{O_2}=140-(55+40)=45$. The pronounced (A-a) P_{O_2} in Patient B indicates the presence of more severe parenchymal disease which interferes with effective gas exchange in the alveoli. In contrast, in Patient A there may be relatively little interference with gas exchange, and the abnormal blood gases are largely attributable to hypoventilation.

The second measurement that can be evaluated is the venous admixture, and this can be determined as the shunt fraction fairly easily, particularly if the patient has an endotracheal tube or a tracheostomy in place. The patient must breathe 100 percent oxygen until equilibration occurs,

TABLE III-4.—*Physiologic Changes in ARDS*

Blood Gases	
$Pa\,O_2$	Decreased or normal
$P_{\bar{v}}O_2$	Decreased or normal
$Pa\,CO_2$	May be decreased, but increases with respiratory failure
(A-a) P_{O_2}	Increased
Shunt fraction	Increased
Lung Mechanics	
Breathing rate	Increased (often rapid and irregular)
Tidal volume (V_T)	Decreased, normal or increased
Vital capacity (VC)	Decreased or normal
Dead space/tidal volume (V_D/V_T)	Increased
Functional residual capacity (FRC)	Decreased
Expiratory reserve volume (ERV)	Decreased (may fall to zero)
Closing volume (CV)	Increased (may exceed FRC)
Forced expiratory volumes (FEV)	Decreased
Other	
Distribution of ventilation	Impaired
Diffusing capacity (DL_{CO})	Decreased
Diffusion/Alveolar volume (DL/VA)	Decreased
Compliance (C_L)	Decreased
Work of breathing	Increased
Inspiratory force	Decreased

$Pa\,O_2$ = arterial oxygen partial pressure
$P_{\bar{v}}O_2$ = mixed venous oxygen tension
$Pa\,CO_2$ = arterial partial pressure of carbon dioxide
(A-a)P_{O_2} = alveolar-arterial oxygen tension difference

which usually takes about 15 minutes, after which an arterial sample is taken. The graph illustrated in Figure III-3 allows a reasonable approximation of the shunt to be read off for measurements made at sea level. An increased shunt percentage is directly correlated with the severity of the lung disease.

A further measurement of value in patients

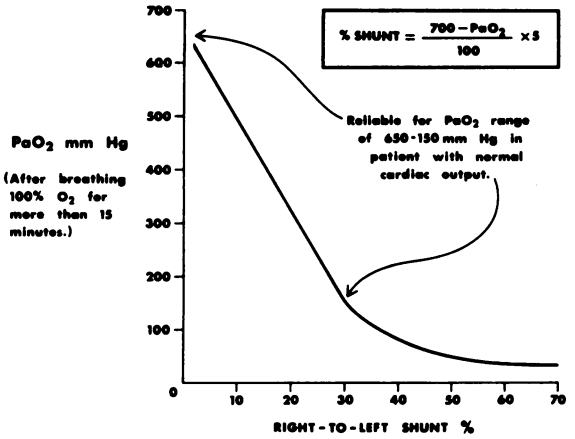

Figure III-3.—This diagram presents the conceptual basis for the estimation of the right-to-left shunt at sea level. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

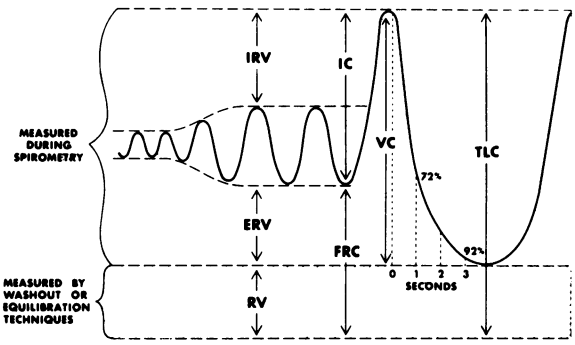

Figure III-4.—Spirogram showing volumes and capacities and forced vital capacity. In severe pneumonia, the total lung capacity (TLC) and vital capacity (VC) are reduced. The tidal volume may be decreased or may be increased. The inspiratory capacity (IC) and the inspiratory reserve volume (IRV) are usually reduced, while the expiratory reserve volume (ERV) and the functional residual capacity (FRC) are notably decreased. The residual volume (RV) is variably affected.

These measurements are not usually made at the bedside with the exception of the tidal volume and the vital capacity. Determination of TLC, RV and FRC can only be made in the laboratory.

Flow rates can be measured at the bedside; these are usually reduced in severe pneumonia. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

with severe hypoxemia who require respiratory support is the mixed venous oxygen tension ($P_{\bar{v}}O_2$).[45] Usually, blood taken from the right side of the heart has a $P_{\bar{v}}O_2$ greater than 35 mm of mercury. If the value is less than this, the tissues are liable to suffer from hypoxic damage. It may be more important to maintain an adequate $P_{\bar{v}}O_2$ rather than to strive for a supposedly adequate Pa O_2, and sometimes the two values do not correlate.[46] Therefore, high pressure gas flow provided by a ventilator may increase the Pa O_2, but by decreasing the cardiac output, it may result in a fall in $P_{\bar{v}}O_2$, which implies a decrease in tissue oxygenation. If a patient is seriously ill with ARDS, a central venous catheter may have the added value of permitting monitoring $P_{\bar{v}}O_2$.

Lung Mechanics. Simple bedside measurements can be made which will provide reliable enough indications of tidal volume, vital capacity and flow rates in patients who can cooperate. Other measurements which may be of value in patient management include the inspiratory force (which is determined by having the patient inspire through a tube linked to a manometer), and, in the case of an intubated patient, the dead space-tidal volume ratio (V_D/V_T).[47]

These values, which are routinely measured on most respiratory care units, can be correlated with the blood gas values and the clinical state to determine whether intubation and respiratory support is necessary, or to help determine whether respiratory support can be discontinued.[48]

Other Physiologic Abnormalities in ARDS

The hallmark of the acute respiratory distress syndrome in severe pneumonia and other parenchymal or interstitial lung diseases includes mismatching of ventilation and perfusion (V/Q abnormality), a decrease in pulmonary compliance (that is, a fall in the amount of gas entering the lung for a given change in transpulmonary pressure) and a reduction in functional residual capacity (FRC).[47]

The functional residual capacity is the volume of gas remaining in the lungs after a normal, unforced expiration (see Figure III-4). In obstructive airway disease, this amount is increased, whereas a decrease occurs with restrictive conditions such as obesity and lying supine or head down. In ARDS, all lung volumes may be decreased, and there is a pronounced reduction in FRC, which correlates with the decrease in Pa CO_2. The fall in FRC is mainly due to decrease in the

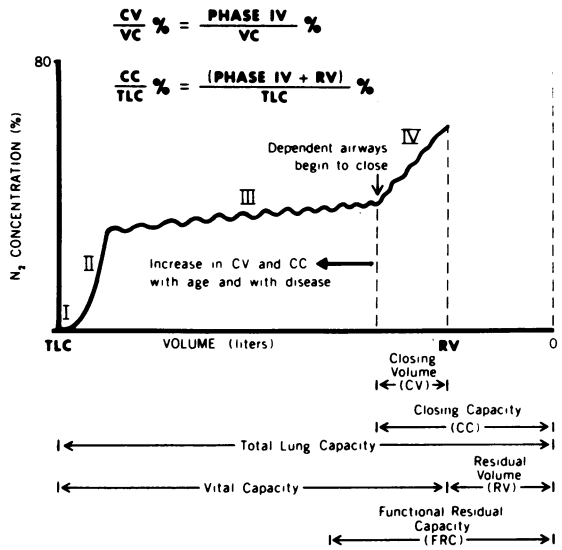

Figure III-5.—Closing volume and closing capacity. Characteristic changes in expired nitrogen concentration which occur during a vital capacity maneuver following an inhalation of 100 percent oxygen.

TLC=total lung capacity; IV=inspiratory volume; VC=vital capacity. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

expiratory reserve volume (ERV), that is, the amount of gas that can be expelled by further effort after a normal expiration. A very dyspneic patient with severe pneumonia may utilize all his ERV, so that no further air can be forcibly exhaled after each expiration.

Damage to the small airways in pneumonia, with the associated mucosal swelling from interstitial inflammation and edema, results in early closing of these airways during expiration, particularly in the dependent lung regions. Since airway closure results in gas trapping, the closing volume and closing capacity are increased in ARDS (Figure III-5). Under such circumstances, atelectasis may occur, and this problem is increased by impaired surfactant production in severe lung infections.

Respiratory Management of Severe Pneumonia

Treatment of the Pathogen

Appropriate antimicrobic management is obviously essential. In some cases, aspiration of involved parenchyma using a transthoracic spinal needle allows early identification of the organism without unacceptable risk to the patient. In other cases, transtracheal aspiration, bronchoscopic suctioning or open or closed biopsy may be needed, if simple sputum examination is unsuccessful. The exact antibiotic or chemotherapeutic agent to be used depends on the clinical situation and microbiological data as discussed by Dr. Galpin.

TABLE III-5.—*Endotracheal Intubation*

A. Reasons for Intubating in Adult Respiratory Distress Syndrome
1. To permit ventilation if patient becomes apneic.
2. To facilitate delivery of oxygen if more than 60 percent is required.
3. To permit suctioning and airway lavage if there is excessive mucus retention.
4. To facilitate the delivery of constant humidity/aerosolization.
5. To facilitate the delivery of other pharmacologic agents.
6. To provide the advantages of respiratory support, e.g. high tidal volume, controlled minute ventilation, control of Pa CO_2, sighing, PEEP.
7. To forestall aspiration.
8. To permit adequate analgesia or sedation in an exhausted patient.
9. To facilitate control of restless or uncooperative or struggling patient.
10. To permit more accurate ventilatory control and monitoring, e.g. V_D/V_T isopleths can be employed if patient is on a volume respirator.

B. Alternatives to Intubation
1. Frequent use of skillfully given IPPB, e.g. for ten minutes every hour.
2. Appropriate use of postural drainage, chest percussion and other techniques in physical therapy.
3. Emplacement of nasopharyngeal airway, to permit frequent endotracheal suctioning.
4. Use of tight fitting pressure mask with high oxygen flow/IPPB; can be used in moderately uncooperative patient.
5. External tank or cuirass respirator.
6. Augmentation of respiration by use of a rocking bed.
7. Stimulation of coughing by a Cofflator machine.
8. Nursing patient in optimal position (e.g. head of bed elevated) to improve oxygenation.
9. Tracheostomy (which is appropriate and preferable to nasotracheal or orotracheal intubation when prolonged respiratory support can be anticipated).
10. Vigorous combination of several of above may obviate need for intubation.

Pa CO_2=arterial partial pressure carbon dioxide
PEEP=positive end expiratory pressure
V_D/V_T=dead space/tidal volume
IPPB=intermittent positive pressure breathing

Oxygen Therapy

Dyspneic or hypoxemic patients require carefully controlled oxygen therapy. In less severe cases, oxygen given by nasal cannula suffices; for each 1 liter flow, about 3 percent oxygen is added to the room air, up to a maximum of about 45 percent, which is achieved with 8 to 10 liters of oxygen. In some patients an aerosol mask is preferable, since this provides the advantages of

humidity, and perhaps 50 to 55 percent oxygen can be delivered. If more oxygen is required to keep the Pa O_2 above 50 mm of mercury, the patient will probably require intubation, and will generally need respiratory support. Table III-5 lists the indications for intubation, and also enumerates alternatives to the use of an endotracheal tube.

There is a danger of producing oxygen toxicity if more than 60 percent oxygen is given for longer than 24 to 48 hours. If it is not possible to maintain a Pa O_2 of 50 with a fractional concentration of oxygen inspired gas (FIO_2) of 60 percent oxygen while on respiratory support, positive end-expiratory pressure (PEEP) may be required.[49] This maneuver results in an increase in the FRC, which may be accompanied by a pronounced rise in Pa O_2. However, there is a danger of PEEP causing a decrease in venous return resulting in a fall in cardiac output. The P_VO_2 may fall under such circumstances, and monitoring this indicator of oxygenation is of value in a very hypoxemic patient.[50]

Patients with severe viral pneumonia may remain dangerously hypoxemic with a Pa O_2 of less than 50 mm of mercury when receiving 70 percent oxygen, with appropriate tidal volumes and minute ventilation, and PEEP of 15 cm of water. Under such circumstances, the use of a membrane oxygenator using extracorporeal circulation should be considered as a possible lifesaving measure.[51] Hyperbaric oxygen therapy has not, as yet, been shown to be of practical value in the management of critically ill patients with ARDS.

Fluid Balance

The lungs in patients with severe pneumonia are heavy, and contain increased amounts of water. Improved oxygenation may result from positive pressure ventilation or from PEEP, in part because these maneuvers decrease the fluid content of the lungs by decreasing venous return and by discouraging exudation from the alveolar capillaries. Diuretic therapy may be of value, but great care is required to prevent adverse changes in fluid balance. The use of a central venous catheter and of pulmonary wedge-pressure measurements by a Swan-Ganz catheter can be extremely helpful. Respirator use often results in an increased secretion of antidiuretic hormone (ADH), which further compounds the difficulties of fluid balance management. Monitoring the measured cardiac output can also be of great help, particularly when using PEEP. If evidence of heart failure develops, cautious use of digoxin may be needed. Frequently, the toxic, hypoxic myocardium is susceptible to arrhythmias, and administration of various antiarrhythmia drugs may be necessary.

Corticosteroids

The role of these drugs in severe pneumonias is quite controversial. Use of steroids leads to increased problems with regard to containment of the infection and management of fluid balance. However, these drugs may have a beneficial effect on the damaged alveolar-capillary membrane, and may prevent or help treat complications of septic shock. Certainly, a patient whose condition is deteriorating while adequate antimicrobial drug therapy is being carried out may be regarded as suitable for a cautious trial of steroid therapy.

Respiratory Drugs

For most patients with severe pneumonia the benefit of bronchodilator therapy is required.[52] Intravenously given aminophylline is usually helpful, the appropriate dose being 5 mg per kg of body weight loading dose followed by 1 mg per kg of body weight per hour as a continuous drip, or the appropriate amount every six hours by bolus administration. Inhalational catecholamines may be given, as long as there is no adverse cardiac effect.

The abnormal secretions should be treated by mucokinetic agents[53] including aerosolized water, or a 2 to 7.5 percent solution of sodium bicarbonate. If the secretions are very viscous, 2 ml of a 20 percent solution of acetylcysteine diluted with an equal amount of sodium bicarbonate can be instilled or nebulized every 1 to 6 hours. A valuable agent is sodium iodide, given by continuous intravenous drip, with a total of 1 to 3 grams per 24 hours.

Some authorities give antibiotics, corticosteroids and other drugs by the inhalational route, but in general these drugs are ineffective or hazardous when given in this fashion.

Prognosis in Severe Pneumonia

The advent of respiratory care units allows intensive, sophisticated management of severe pneumonias. Undoubtedly skillful care results in improved rates of survival, but unfortunately many patients with severe pulmonary infections are elderly or debilitated, or have abnormal lung

architecture or impaired immunologic mechanisms. The presence of such adverse circumstances notably lowers the success of even the most skillful and sophisticated management, and clinical judgment is required to determine whether the complex and dangerous modalities involved in total respiratory care are justified for an individual patient with overwhelming pneumonia.

DR. OILL: Dr. Paul Selecky will now discuss two separate respiratory problems. The first is pulmonary hemorrhage secondary to earlier infection in the lung. The second is the processes that involve the neurogenic control of respiration and may manifest as alveolar hypoventilation.

The final speaker for this part of the symposium is Dr. Jerome Schofferman, who will address himself to the evaluation, pathophysiology and management of anaphylaxis.

Hypoventilation Syndrome and Pulmonary Hemorrhage

PAUL SELECKY, MD:* Various types of infectious disease emergencies can involve the respiratory system, most of these being the result of a primary infection of the lung by some pathogen. These are described elsewhere in this symposium. Two unique situations that may present to the emergency department should be mentioned separately. One special problem is the occurrence of an acute pulmonary hemorrhage secondary to an earlier infection in the lung. Another is the phenomenon of *alveolar hypoventilation* (hypoxemia and hypercapnia) secondary to a disturbance in the neurogenic control of breathing which is caused by some infectious process. In brief, the latter situation pertains to the patient who presents with dyspnea and abnormal arterial blood gas values despite normal findings on a roentgenogram of the chest.

Pulmonary Hemorrhage

Massive hemoptysis is a frightening event for both patient and physician. Even the slightest amount of blood in the expectorated sputum is of great concern. Physicians in the emergency department, however, usually do not get involved unless the amount of bleeding is significant. By definition, this has been categorized as hemoptysis that produces more than 600 ml blood in 24 hours.

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TABLE III-6.—*Management of Pulmonary Hemorrhage*

1. Protect airway: erect position, artificial airway.
2. Support vital functions: oxygen, transfusions.
3. Stop bleeding: airway care, treat any clotting disorder.
4. Identify bleeding site: chest roentgenogram, early bronchoscopy.
5. Thoracotomy for massive bleeding (greater than 600 ml/24 hrs).

The cause is most commonly the breakdown of lung tissue secondary to a chronic infectious process, such as bronchiectasis, pulmonary tuberculosis or fungal disease, and lung abscess.[54] Bronchogenic carcinoma can also be a cause of hemoptysis, but this usually does not cause a pulmonary hemorrhage, except occasionally terminally.

There is often difficulty in quantitating the amount of expectorated blood. The findings on a roentgenogram of the chest are not always helpful—a small abscess can be the cause of a large amount of bleeding, while grossly abnormal findings on a roentgenogram may represent a presently quiescent condition. The basic approach to the treatment of pulmonary hemorrhage, therefore, is to admit the patient to hospital and observe him closely.

Guidelines for the acute management of this problem are depicted in Table III-6. The basic tenets of protecting the airway and supporting vital functions are the keystone. In most patients endotracheal intubation is not needed, but clinical judgment must prevail. Blood in the airway can be very irritating, resulting in violent coughing, such that intubation can sometimes be quite beneficial for suctioning even though assisted ventilation may not be necessary. If progressive hypoventilation develops, however, a respirator should be employed. The other modalities of good respiratory care must also be utilized—bronchodilators, humidification and postural drainage. Chest percussion should most likely be avoided for fear of perpetuating the bleeding, although this has not been substantiated.

Recent reports in the surgical literature have supported early thoracotomy for the treatment of massive hemoptysis.[55,56] For this reason, bronchoscopy should be used early in the patient's course to try to identify the anatomic site of bleeding.[57] This applies to a patient with minimal hemoptysis as well, because it is generally unpredictable whether in such a patient a life-threatening hemorrhage may occur hours later. Bronchoscopy at that time is often unsuccessful

in locating the bleeding site because the blood is scattered throughout the tracheobronchial tree.

The mortality in patients with massive hemoptysis varies with the duration and intensity of the blood loss, but has been reported to exceed 75 percent when the bleeding of 600 ml occurred within 16 hours.[55,56] With early lung resection in these patients, the mortality decreased to 23 percent, indicating that nonoperative management was inadequate. Generally, patients with hemoptysis will improve with basic airway care alone. The occasional patient with brisk bleeding, however, may profit from early thoracotomy, provided that the anatomic bleeding site has been identified, and that the patient has adequate pulmonary reserve to tolerate lung resection.

Alveolar Hypoventilation

Alveolar hypoventilation is diagnosed by laboratory evidence of disordered gas exchange, specifically, hypercapnia and hypoxemia by arterial blood gas values while breathing room air. This can be the result of a multiplicity of disorders, including primary lung diseases and disorders of the control of breathing. The latter refers to problems involving the neural pathway from the respiratory center in the central nervous system (CNS), down the nerve roots, to and including the respiratory muscles themselves. It is this less common cause of alveolar hypoventilation that I will focus on.

Problems with the control of breathing from infectious causes include any infection that can result in severe CNS depression—for example, encephalitis, meningitis, brain abscess or a generalized sepsis. The group of diseases that are described in this section present in yet another way. Briefly, the typical presentation is that of a patient who enters the emergency department with complaint of dyspnea, is unable to inspire effectively, or perhaps aspirates every time he tries to swallow. He is generally weak and quite frightened. He may have noticed some blurred vision or diplopia or perhaps some distal paresthesias. On examination the patient is found to be mentally alert, but has diffuse motor weakness and nasal speech, and is perhaps somewhat ataxic. Findings on studies of arterial blood gases show hypercapnia and hypoxemia, but on examination of the lungs and on a roentgenogram of the chest no abnormalities are seen. By definition, the patient has alveolar hypoventilation. The problem now is to consider what infectious disease states must be included in the differential diagnosis of this presentation—that is, an alert patient in whom there are normal findings on a chest examination and who is perhaps diffusely weak and is hypercapneic and hypoxemic.

TABLE III-7.—*Infectious Causes of Hypoventilation Secondary to Neuromuscular Dysfunction*

Polyneuritis
Guillain-Barré syndrome
Acute poliomyelitis
Rabies
Neurotoxin
Tetanus
Botulism
Tick paralysis
Diphtheria
Neuromuscular blockade
Complications of antibiotic use

Table III-7 describes three categories of infections that can present as alveolar hypoventilation. These include the neuromuscular weakness that can occur as the result of (1) a polyneuritis or similar disturbance (Guillain-Barré syndrome, acute poliomyelitis and rabies), (2) the effects of a neurotoxin either from direct infection of an organism (tetanus, tick paralysis, diphtheria) or ingestion of toxin-contaminated foods (botulism), or (3) a neuromuscular blockade that can occur with the use of certain antibiotics.

Polyneuritis

Guillain-Barré syndrome. This is a clinical entity that has no identifiable cause, although it has commonly been seen during the convalescent phase of an upper respiratory infection or gastroenteritis, suggesting a viral origin. Characteristically, the patient presents with a symmetrical muscle weakness and tenderness that starts distally in the legs and can ascend in a progressive manner—in other words, ascending paralysis. In many patients cranial nerve involvement may also develop. Distal paresthesias have been described, as well as stocking-glove sensory losses.[58] The patient is afebrile; studies of spinal fluid show an elevated protein level with very few cells (predominantly mononuclear).

Most of such patients are moderately incapacitated by weakness, but as many as 15 to 40 percent may progress into respiratory failure and possible death unless full respirator support is carried out.[59,60] The physician's immediate responsibility is to follow the patient closely to avert such respiratory failure. The appropriate measurements and treatment of this hypoventila-

tion will be discussed below. There is no specific treatment for this disorder. It is generally a self-limited disease, but may have a prolonged recovery period, lasting six months to two years.

Acute poliomyelitis. This is a generalized viral illness which typically leads to destruction of the motor cells in the spinal cord and brain stem with subsequent nerve degeneration and flaccid paralysis. Before 1956 there were as many as 50,000 cases each year.[61] The advent of orally given polio vaccine has fortunately made this illness a rarity; less than 50 cases are now being recorded a year.[62] Despite public health efforts, occasionally a child escapes adequate immunization and may present with the disease. Initial symptoms include a flu-like illness with fever for 2 to 3 days, followed by increasing headache, muscle soreness and stiff neck. This may then resolve, but in a small group may be followed several days later by a flaccid and asymmetrical paralysis, commonly involving the lower extremities and trunk; in about 15 percent of patients bulbar palsy develops. Spinal fluid examination results show a lymphocytosis but normal protein level, in contrast to Guillain-Barré syndrome. Diagnosis is generally made on clinical evidence, but can be confirmed by a four-fold rise in neutralizing antibody titer. Treatment is generally supportive. Evidence of respiratory difficulty requires vigorous treatment; mortality in such patients can reach 50 percent.[61]

Rabies. This disease is included in this series of respiratory emergencies, although the primary role of the physician lies in preventing the disease long before any respiratory problems may arise. This results from the fact that the encephalitis caused by this neurotropic virus is universally fatal (with one exception[63]) unless prophylactic treatment is administered immediately upon suspected exposure to the virus. The disease is acquired by contact with the saliva of an infected animal either by bite or lick. The incubation period lasts about two weeks, but has been described as lasting one year. The active infection presents as headache, fever, nausea and vomiting, paresthesias, muscle spasms and seizures that proceed to death in 5 to 14 days. The severity depends on the dose of the inoculum and its proximity to the CNS. Once established in the nerve root, fatal CNS involvement is unavoidable.

The only successful treatment is to inoculate the patient with antiserum and vaccine at the time of exposure. Approximately 600,000 people are bitten each year in the United States by animals that potentially are infected. About 35,000 are treated with the vaccine; 3,000 also are given the equine antiserum (and in about 45 percent of these serum sickness develops).[64] The success of this therapy is noted by the low incidence of rabies deaths (two per year).[62]

Treatment must be started immediately, ideally within 24 hours of exposure.[65] Each physician must, therefore, be acquainted with the indications and methods of treatment, which have been outlined by the World Health Organization.[66-68] In brief, any bite by a wild skunk, fox, raccoon or bat requires immediate treatment with both rabies vaccine and antiserum. Bites by domestic animals must be evaluated individually. The arguments against the use of equine antiserum because of the fear of serum sickness are now resolved with the availability of human rabies immune globulin.[64] Suggested treatment regimens include: local wound care, active immunization with duck embryo vaccine (1 ml given subcutaneously daily for 21 days, plus two boosters at 10 and 20 days after last daily dose), and human antiserum injected in the bite and systemically (15 to 40 units per kg of body weight given intramuscularly).

Neurotoxin

Tetanus. This is an anaerobic Gram-positive bacillus infection due to Clostridium tetani resulting in neuromuscular dysfunction secondary to the release of a neurotoxin. It is an uncommon problem since the advent of tetanus immunization (an average of 175 cases each year)[62] but can occasionally be seen in heroin addicts or in non-immunized persons. The disease occurs as the result of bacterial contamination of an injury or wound which has an appropriate anaerobic condition (for example, tissue necrosis), allowing the spore forms to develop into the toxin-producing vegetative forms. Corrosive metals, soil and animal feces are common sources for Clostridium tetani inoculation. Despite partial healing of the initial injury, the patient presents some 6 to 14 days later with signs of neuromuscular hyperirritability-hyperreflexia, muscle spasms (trismus, dysphagia, risus sardonicus) and dysautonomia (labile hypertension, sweating, tachycardia). Depending on the amount of circulating neurotoxin, this may ultimately progress to opisthotonos, seizures and death due to asphyxia. These symptoms are the result of synaptic inhibition by the

blood-borne toxin as it becomes bound to nerve tissue. Diagnosis is based largely on clinical evidence; the organism is very difficult to grow in culture.[69]

Treatment must be vigorous—the mortality can exceed 50 percent in severely infected patients especially at the extremes of age.[61] Public Health data record an average of 100 deaths a year for the nation.[62] Airway care is vitally important because of the laryngeal and chest wall tetanic spasms as well as the aspiration of secretions that can occur. Indications for tracheostomy and respirator support will be discussed below. Immediate treatment of the infection should follow these guidelines:[70]

- immediate passive immunization with antitoxin (human tetanus immune globulin, 6,000 to 10,000 units given intramuscularly and into the wound site);
- antibiotic therapy with intravenously given penicillin (5 to 10 million units per day) or tetracycline (500 mg given intravenously every six hours);
- wound debridement one to two hours *after* passive immunization has been completed;
- active immunization with alum-precipitated tetanus toxoid (0.5 ml given intramuscularly initially and again in six weeks and six months) following recovery;
- avoid repetitive intramuscular or subcutaneous injection which may precipitate muscle spasms due to the pronounced neuromuscular irritability.

Subsequent treatment of the muscle spasms has been achieved with various relaxants, including diazepam, chlorpromazine and occasionally curare.

Prevention has been the mainstay in decreasing the incidence of tetanus. If there is any doubt concerning the patient's immunization status at the time of a crush injury, recommended prophylactic treatment includes administration of: human tetanus antitoxin (250 to 500 units given intramuscularly), tetanus toxoid booster (0.5 ml given intramuscularly) and penicillin or tetracycline.[69]

Botulism. This is an uncommon syndrome with less than 50 cases being reported yearly.[62-71] The classical disease is not true infection, but rather a food poisoning that results from ingesting improperly preserved (and uncooked) vegetables, meat and fish that are contaminated with Clostridium botulinum (types A, B, E). However, occasionally an injury or wound may harbor the organism and result in the same clinical entity. The neurotoxin produced by the growth of this organism in food is readily absorbed and is transported to the myoneural junction where it acts to decrease the release of acetylcholine. The result is diffuse weakness in both smooth and striated muscles. About 12 to 48 hours after ingestion, depending on the dose of toxin received, the patient may complain of nausea and vomiting, diplopia, dysphagia and nasal speech. On examination a diffuse weakness in the trunk and all extremities, as well as ptosis and extraocular palsies is found. A distinguishing feature is the smooth muscle involvement, often presenting as dilated pupils, intestinal ileus and urinary retention. With profound paralysis, respiratory failure and coma may occur. Mentation is intact and there is no sensory involvement. (See Addendum.)

Diagnosis is made from findings on the clinical examination and the history of ingesting rancid-tasting and uncooked preserved food (the toxin is heat-labile and easily destroyed by heat). Analysis of the contaminated food and patient's serum for presence of toxin should be done for confirmation of diagnosis. Anaerobic culture of wounds is essential. Treatment consists of supportive measures plus administration of trivalent (ABE) botulinus antitoxin (20,000 to 40,000 units given intravenously) for symptomatic patients.[72] Despite comparable exposure, such as several members of a family eating the same meal, in less than half the patients will symptoms develop. All should receive a gastrointestinal purge. Careful observation for respiratory insufficiency is mandatory and preparation for early tracheostomy is crucial. Mortality from respiratory failure can be as high as 30 to 50 percent.[72]

Tick paralysis. Another disease-state that can present as diffuse weakness occurs as the result of a neurotoxin found in tick saliva. The patient is bitten by a wood or dog tick while hiking or camping; the tick then attaches itself to the skin for 5 to 7 days before symptoms develop. Clinically, the patient presents with a lower extremity weakness that can ascend to produce a diffuse flaccid paralysis. Results of sensory examination and spinal fluid studies are normal, in contrast to Guillain-Barré syndrome. Diagnosis is made by finding the tick imbedded in the skin, often on the scalp. Removal is usually followed by complete recovery in 24 hours. If unrecognized and un-

treated, mortality can range as high as 10 percent.[73] Physician awareness, therefore, is the chief link in determining the outcome of this totally reversible disease.

Diphtheria. This is a relatively rare disease which traditionally presents as a febrile, mild pharyngitis that causes the formation of a gray pseudomembrane on the pharynx. The more common cause of respiratory difficulty in this disease is upper airway obstruction that can occur from the pharyngeal web, and that aspect of the disease has already been discussed. It is included in this series because of the circulating neurotoxin that can be produced by the organism (Corynebacterium diphtheriae), causing a distal symmetrical weakness. Intercostal muscles and the diaphragm may also be involved, resulting in respiratory failure.

In most patients the neurotoxin is released only in the throat, but in 6 to 20 percent the diffuse polyneuritis may also develop.[61] The pharyngeal sensory loss can progress to include the cranial nerves in 5 to 12 days, followed by ciliary muscle paralysis and blurred vision by the end of the third week. Diffuse weakness can occur as late as two months after the initial infection. Active immunization procedures have fortunately made the disease uncommon (an average of 200 cases a year).[62] Occasional major outbreaks, however, continue to occur.[74] Treatment is generally supportive. Antibiotics (penicillin, tetracycline, erythromycin) and equine diphtheria antitoxin are administered for the pharyngeal stage. Antitoxin is ineffective for the treatment of the diffuse weakness because the neurotoxin has already become bound to the nerve. The period of recovery may be quite prolonged. The outcome is largely dependent on the quality of the respiratory support, although cardiac involvement with the toxin portends a poor prognosis. National mortality figures show an average of 20 to 40 deaths per year.[62]

Neuromuscular Blockade

Several antibiotics have been shown to be capable of producing significant neuromuscular blockade. The effects can vary from a mild weakness to a diffuse myasthenic-like paralysis with apnea and death. Perioral paresthesias, diplopia, ptosis and dysphagia, as well as smooth muscle effects (ileus), have also been described. The antibiotics in which this has been reported are listed in Table III-8. These are basically two groups of antibiotics: (1) *aminoglycosides* which produce a competitive blockade at the motor endplate that can be reversed with neostigmine or calcium and (2) the *polymyxin* group (B, E) which establish a noncompetitive blockade and cannot be eliminated with neostigmine (but are reversible with calcium). Other antibiotics have been associated with neuromuscular weakness (tetracycline, sulfonamides), but respiratory paralysis has not been described.[75]

TABLE III-8.—*Antibiotics That Can Cause Muscle Weakness and Hypoventilation Secondary to Neuromuscular Blockade*

Aminoglycosides
Gentamicin
Kanamycin
Dihydro/Streptomycin
Neomycin
Viomycin
Polymyxins
Polymyxin B
Polymyxin E (colistimethate)
Miscellaneous
Tetracyclines
Sulfonamides

Among the aminoglycosides, physicians are more likely to observe this complication with gentamicin because of its more common use,[76] although it can also be seen with streptomycin,[77] neomycin,[78] kanamycin[79] and viomycin.[80] The myasthenic-like effects of the polymyxin group also have been well described.[81]

The blockade caused by both groups of drugs is not dose-related and as such has occurred after only one dose, as well as after 45 days of therapy. Similarly, it can cause sudden apnea within one hour after drug administration or as long as 26 hours later.[81] The effects can take many forms, although a typical reaction might begin with dysphagia an hour after the drug is administered, followed by perioral paresthesias, diplopia and progressive dyspnea. Within 90 minutes the patient can be totally apneic. In a milder form, it can be difficult to distinguish these clinical features from myasthenia gravis or the Eaton-Lambert syndrome. Findings of an electromyogram are occasionally helpful.

Various experiences with this type of antibiotic-induced neuromuscular blockade have indicated that certain clinical factors might have predisposed the blockade, such as the additive effects of using several of these drugs in the same patient. Other factors included the antecedent existence of renal failure, hypocalcemia, other neuromuscular

TABLE III-9.—*Differential Diagnostic Features of Infectious Causes of Neuromuscular (NM) Weakness*

Disease	*Motor Weakness*	*Sensory*	*Other*
Guillain-Barré ..	Distal, symmetrical; can be bulbar	Paresthesias; ↑ proprioception, ↓ touch	↑ CSF protein; dysautonomia
Poliomyelitis ...	Asymmetrical	Normal	↑ CSF cells; fever
Botulism	Diffuse, symmetrical; cranial nerve; ileus	Normal	History of food ingestion, vomiting
Tick paralysis ..	Distal, symmetrical, ataxia	Normal	CSF normal; tick bite
Diphtheria	Distal, symmetrical; cranial nerve	Reduced touch/pain/proprioception	History of pharyngitis with web
NM blockade ...	Diffuse; cranial nerve; ileus	Paresthesias	History of drug exposure

CSF = cerebrospinal fluid

disorders (myasthenia gravis) or the administration of the drug onto a serosal surface (sinus irrigation, peritoneal lavage).[76,82] When one of these drugs must be used under such circumstances, the patients should be observed closely with repeated tests of muscle strength, much as a patient with Guillain-Barré syndrome is monitored, in order to avoid sudden respiratory embarrassment.

Supportive management of this syndrome is vital; on occasion, the blockade can be reversed. Paralysis secondary to the aminoglycosides has improved after the administration of calcium gluconate (25 grams given intravenously) or neostigmine (0.5 to 2 mg given intramuscularly or slowly intravenously; total dose less than 5 mg).[61,78,79] Unpleasant side effects of the neostigmine may require pretreatment with atropine.

The effects of polymyxin should be treated with intravenously given calcium only; neostigmine is ineffective and in fact may potentiate the blockade.[81] These antidotes are helpful but often do not obviate the need for respirator support.

Reviewing these many disease states shows that the neuromuscular weakness and respiratory paralysis can present in a similar manner. Treatment at times must be very specific, such that precise diagnosis is important. The clinical history will often be the greatest help, for example, ingesting rancid food, use of suspected antibiotic, recent camping trip. Other helpful differential features are described in Table III-9.

Respiratory Support

The treatment of respiratory failure has been well described by many authors[83,84] and therefore there will be no attempt to discuss it in depth here. The basic points of good respiratory care, however, should be emphasized. These include: (1) establishing a patent airway, (2) oxygen therapy and (3) determining the need for assisted ventilation, that is, respirator support.

Airway Care

The foundation of adequate support for patients with respiratory difficulty is to ensure a good airway. Many times this can be accomplished with proper positioning of the patient, or with the use of an oral airway to keep the tongue forward or a nasopharyngeal tube.[85] When this is not possible, or if the patient continues to aspirate saliva, an endotracheal tube should be passed under direct vision. The patient can then be supported with proper airway humidification and suctioning for periods of 3 to 7 days without serious sequelae.[86,87] Many of the symptoms of the diseases described here can improve or completely resolve during this interval, allowing the physician to extubate the patient.

Tetanus should be mentioned separately because of the laryngeal spasms that can occur. If these cause persistent respiratory insufficiency, a tracheostomy should be carried out. In other diseases, a tracheostomy might not be necessary unless an artificial airway is required for more prolonged periods. Meticulous tracheostomy care is then mandatory to avoid serious complications.[88]

Oxygen Therapy

Hypoxemia is a necessary part of alveolar hypoventilation, but might not be so severe as to cause significant dysfunction. Supplemental oxygen is easily administered, but a physician should have specific goals in mind, such as to supply the amount of oxygen necessary to maintain a $Pa\,O_2$ of 60 to 80 mm of mercury. A higher $Pa\,O_2$ is unnecessary, especially if it runs the risk of oxygen toxicity secondary to high inspired oxygen concentrations (greater than 50 percent).

Assisted Ventilation

It is often difficult to assess whether a patient should be intubated and placed on a respirator. This is especially troublesome in a patient with neuromuscular weakness, for example, with Guillain-Barré syndrome, in whom there might be moderate respiratory impairment, but in whom reasonable arterial blood gas values are still being maintained. Respiratory efforts are often at a high energy cost in such a patient, in which case ventilatory assistance would be quite helpful. At the same time, however, intubation and the use of respirators can carry a significant morbidity.[86,89,90]

The solution for this dilemma lies in making repeated physiologic measurements to assess the need for respiratory assistance. Some basic guidelines are listed in Table III-10. It is especially helpful to make frequent measurements of vital capacity. A trend of progressively lower vital capacity volumes is more helpful in indicating the need for respirator support than waiting for the rock-bottom vital capacity of 10 ml per kg of body weight. This measurement requires a conscious, vigorous effort by the patient, such that both muscular strength and patient cooperation are assessed. Other additive features such as increased airway secretions or cardiac arrhythmias increase the need for respirator support.

As the condition of the patient improves with some return of muscular strength, similar guidelines can be used to decide when to discontinue the respirator and remove the tracheostomy.[91,92] In brief, it is wise to gradually wean the patient from the respirator by allowing him to breath spontaneously for progressively longer periods, returning to the respirator in the interim. When he becomes safely independent from the respirator for 24 hours, it is likely that the tracheostomy can be removed.[88]

TABLE III-10.—*Clinical Indications for Respirator Support*

1. Vital capacity less than 10 ml/kg
2. Pa CO_2 greater than 50 mm Hg and rising (pH less than 7.25)
3. Oxygenation ratio (Pa O_2/% inspired O_2) less than 1.5
4. Clinical factors:
   - Respiratory rate greater than 40/min
   - Copious secretions
   - Hypotension; malignant arrhythmias
   - Mental obtundation

Pa CO_2 = arterial partial pressure carbon dioxide
Pa O_2 = arterial partial pressure oxygen

Anaphylaxis

JEROME SCHOFFERMAN, MD:* The treatment of many infectious disease problems includes the use of antibiotics. As always, we must be prepared to recognize and treat any side effects or complications that might arise from the therapy itself. The use of antibiotics is no exception. Certain antibiotic-induced problems are specific for that particular drug but one symptom complex, anaphylaxis, might be seen after the administration of any antibiotic. The list of agents that have caused anaphylaxis is quite long and includes many antibiotics, insect stings, snake bites, horse serum, contrast media, dextran, insulin, local anesthetics, certain foods and many, many more.

In the following discussion, I would like to reacquaint you with the signs and symptoms of the anaphylactic syndrome, the pathophysiology and the various treatment modalities available.

At the outset it may be prudent to repeat a warning. It is important to take careful history from each patient to whom you might administer any drug. Be alert for past adverse reactions and try to elicit the details of the reaction. Many patients believe they are allergic to a drug because they experienced nausea or diarrhea after taking it. Play it safe, however. An ounce of prevention is worth a pound of epinephrine.

It is clinically useful to consider anaphylaxis as a symptom complex that occurs within minutes to hours after exposure to an antigen in a suitably immunized host.[93] The symptoms are due entirely to the actions of the chemical mediators released during the reaction on various target organs[94] (see Table III-11). The particular end organ response will vary from one person to the next. In some patients, subjective symptoms may herald the onset of the entire syndrome before objective signs appear. A patient may just describe a feeling that "something is wrong." Others might relate a feeling of fright or a feeling of retrosternal tightness. Itching in or around the eyes, the throat or the ears may be described. We have seen several patients in whom the initial symptom was a feeling of overall warmth, soon followed by widespread itching and finally by hypotension or bronchospasm. At times dyspnea, stridor, hoarseness or a "lump" in the throat due to upper airway edema may be the initial problem, as might dizziness or faint secondary to hypotension.[94]

The symptom complex of anaphylaxis has been

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TABLE III-11—*The Symptom Complex of Anaphylaxis**

System and Reaction	*Symptoms*	*Signs*
Respiratory tract		
Rhinitis	Nasal congestion and itching	Mucosal edema
Laryngeal edema	Dyspnea	Laryngeal stridor; edema of cords
Bronchospasm	Cough; wheezing; sensation of retrosternal oppression	Cough; wheezing; rales; respiratory distress; tachypnea
Cardiovascular system		
Hypotension	Syncope; feeling of faintness	Hypotension; tachycardia
Arrhythmia	.....	Electrocardiographic changes: Nonspecific S-T segment and T-wave change; nodal rhythm; atrial fibrillation
Cardiac arrest	.....	Absent pulse; electrocardiographic change: Asystole; ventricular fibrillation
Skin		
Urticaria	Pruritus; hives	Typical urticarial lesion
Angioedema	Nonpruritic swelling of an extremity, perioral or periorbital region	Edema frequently asymmetrical
Gastrointestinal system		
....	Nausea; vomiting; abdominal pain; diarrhea	.....
Eye		
Conjunctivitis	Ocular itching; lacrimation	Conjunctival inflammation

*From: Kelly JF, Patterson R: Anaphylaxis: Course, mechanisms and treatment. JAMA 227:1431-1436, Mar 25, 1975, Copyright 1974, American Medical Association.

clearly summarized by Kelly and Patterson.[93] The skin is often the first organ involved. Diffuse erythema, a feeling of generalized warmth, itching, urticaria or angioedema may be present singly or in combination. The urticarial lesions can be local or generalized and are usually quite pruritic. Moreover, coalescence of the lesions forming giant hives has been reported.[94] Angioedema may involve the face or extremities in an asymmetric fashion but if soft palate, epiglottis, larynx or trachea are involved, life-threatening upper airway obstruction (UAO) may ensue.

Eye involvement with tearing, itching and redness is not uncommon. This conjunctivitis is rarely serious but could be a warning of subsequent, more ominous physiologic sequelae.

Gastrointestinal complaints might include nausea, vomiting, abdominal pain or diarrhea which is rarely bloody. Again, these manifestations are usually not serious.

The life-threatening manifestations of the anaphylactic syndrome involve the respiratory tract or the cardiovascular system, or both. Rhinitis might be an early symptom and is usually of little consequence. UAO is the most feared problem. It can involve many areas of the upper airways and develop quite suddenly. The symptoms have been previously mentioned. Physical findings include inspiratory stridor, a prolonged inspiratory phase of respiration or pronounced retraction of accessory muscles of respiration. Simple direct visualization of the palate and uvula may show the pronounced edema. Bronchospasm is more commonly seen. Cough, wheezing or a feeling of tightness behind the sternum are typical complaints. Expiratory wheezes will be present but if bronchospasm is severe and air flow limited, wheezes may be minimal or absent.

Cardiovascular manifestations can involve the heart or peripheral vascular system. Hypotension, when present, seems to be due to a reduction in effective plasma volume secondary to escape of fluid from the intravascular compartment and a resultant decrease in cardiac output.[95] Hypotension may also be a sequela of profound hypoxia. Various electrocardiographic abnormalities have been described including atrial fibrillation, other supraventricular arrhythmias, transient left bundle branch block, ventricular fibrillation and even asystole.[95-97] ST segment and T wave abnormalities can mimic myocardial ischemia or injury[95,96] and at times elevations of cardiac enzymes have been present.[96]

Although the signs or symptoms of the anaphylactic syndrome may be characteristic, certain other disease processes should be considered in

the differential diagnosis. The common fainting episodes (vasovagal reaction) secondary to any painful injection and the pseudoanaphylactic syndrome following inadvertent intravenous administration of procaine penicillin[98] have to be considered. Certain viral illnesses produce a rash which may have been initially overlooked, but becomes clinically evident coincidentally following administration of a drug or antibiotic. Some drugs produce toxic erythema. Phenothiazine injections can cause hypotension. Several drugs may precipitate wheezing in patients with the "aspirin sensitivity syndrome."[99]

The period of time from exposure to the antigen to onset of symptoms is variable and depends on the individual patient, route of administration and dosage. After oral ingestion of antigen, symptoms might occur after only five minutes instead of several hours later, as one might anticipate. Generally, patients present with complaints soon after parenteral exposure but again the time course is variable. A general rule might be to observe all patients who have received medications in an outpatient setting for 30 to 60 minutes before discharge.

The duration of symptoms is also unpredictable. Reactions may resolve almost immediately with therapy but at times can linger for 24 to 48 hours despite seemingly adequate treatment. In addition, attacks that appear to have subsided do recrudesce. Consequently, patients who suffer severe systemic reactions should be admitted to the hospital and observed for at least 12 to 24 hours after all signs and symptoms have cleared before discharge. Careful judgment is necessary for patients with less severe attacks. Mild reactions may be harbingers of more life-threatening events and, therefore, all patients should be observed for several hours. Before discharge, a physician or nurse must meticulously explain to the patient the signs and symptoms of the entire anaphylactic syndrome. The patient should be instructed to return to an emergency facility immediately if any occur. It is also wise to prescribe sufficient oral medications (see below) to be taken during the following 24 to 48 hours.

In order to logically approach the therapy of anaphylaxis, we must briefly review the pathophysiology.[93,94] The first stage of an anaphylactic reaction occurs at some time, perhaps forgotten or unknown, when the host is originally sensitized to an antigen. Specific antibodies (IgE) are formed which attach to the surface of mast cells and basophils. Reexposure to the foreign substance results in antigen bridging of two IgE molecules on the cell surface with resultant membrane changes and release of the pharmacologic mediators.[94]

Histamine is the chemical mediator most closely linked to human anaphylaxis. It is found in mast cells, basophils, platelets and the parietal region of the stomach.[94] In man, histamine causes bronchial constriction[93] which may be a vagal reflex rather than a direct action on smooth muscle.[94] Intravenous administration of histamine does cause increased capillary permeability, vasodilation, hypotension, headache and flushing.[93,94]

Slowly reacting substance of anaphylaxis (SRS-A) is also thought to play a role in human anaphylaxis.[93,94] It too causes contraction of human bronchial smooth muscle and at least *in vitro* may potentiate the smooth muscle actions of histamine.

Bradykinin, serotonin and prostaglandins have all been implicated in the animal model of anaphylaxis but the role of these substances in the human syndrome is not fully clarified. The role of eosinophil chemotactic factor (ECF-A) is also not completely understood.[94]

It is important to note that the immunological release of chemical mediators is closely linked to levels of cellular cyclic adenosine monophosphate (c-AMP).[93] However, other pathways for mediator release are suggested as well. Increased levels of c-AMP tend to decrease release of histamine and SRS-A after antigen challenge while decreased c-AMP levels favor mediator release. Drugs such as the beta-agonists increase c-AMP levels and thereby decrease mediator release and alpha-agonists tend to do the opposite. These important actions lead us into a discussion of the therapy of anaphylaxis.

Initial treatment for this syndrome must be directed toward life-threatening manifestations. Immediate attention to the airway is most essential. Upper airway obstruction must be dealt with promptly. Early therapy with epinephrine may improve upper airway edema but if obstruction progresses, tracheostomy should be strongly considered. It is often difficult to carry out endotracheal intubation in this situation. In fact, repeated attempts at endotracheal intubation may further aggravate airway obstruction. Local application of epinephrine or steroids does not appear to be helpful. Oxygen should be used as necessary. It is essential to evaluate the condi-

tion of a patient closely both clinically and with arterial blood gas analysis to ensure adequate ventilation and perfusion.

Hypotension commonly responds to fluid infusion or elevation of the legs, or both. Use of epinephrine is definitely indicated and the response may at times be dramatic. Repeated doses may be needed. Alpha adrenergic drugs should be avoided if possible. Rarely, isoproterenol may be indicated.

From these initial recommendations, it is clear that epinephrine is the cornerstone of therapy and remains the drug of choice to treat all aspects of the anaphylactic syndrome. Route, dosage and frequency of administration must be judged according to the clinical setting. Epinephrine acts at two levels. It interferes with further mediator release and antagonizes the effect of the mediators on target organs. For most patients, 0.3 to 0.5 ml of 1:1,000 epinephrine is recommended. Subcutaneous injection is effective if the patient is not hypotensive or notably vasoconstricted. However, if absorption from a subcutaneous site is inadequate or questionable, deep intramuscular injection is preferred. With hypotension or shock, 0.1 ml of epinephrine diluted in 10 ml of saline solution should be administered intravenously.

The antihistamines are also useful. Diphenhydramine is used most often and the route is dependent on the clinical features. Antihistamines act as competitive inhibitors of histamine at the target organ[93] and do not interfere with histamine release. A dose of 50 to 80 mg (maximum of 5 mg per kg of body weight per 24 hours) may be given every six hours orally or intravenously as indicated.[100] If moderate or severe bronchospasm is present, use of antihistamines may be dangerous because of their sedative properties.

Aminophylline should be added to epinephrine when moderate or severe bronchospasm is present. As in the treatment of any acute asthmatic attack, a loading dose of 375 mg[101] or 5.6 mg per kg of body weight[102,103] may be given over 7 to 10 minutes intravenously and followed by continuous drip therapy of 0.9 mg per kg of body weight per hour[101] or intermittent boluses of 250 mg every four to six hours. Oral bronchodilators are also useful for mild bronchospasm or for temporary maintenance therapy after the initial attack has subsided.

Corticosteroids are not useful for the acute situation. They are usually reserved for severe attacks unresponsive to the above modes of therapy. Dosage has been arbitrary, a dose of 60 to 125 mg of methylprednisolone intravenously every six hours appears efficacious.

Local therapy for anaphylaxis is directed toward prevention of further absorption of the antigen, and must be instituted early for maximum benefit. One such local measure would be placing a constricting band proximal to the site of antigen inoculation, such as an insect sting or injection. Alternatively, or in addition, local instillation of epinephrine might be beneficial.

Patients must also be carefully warned to avoid the suspected antigen in the future. Consultation with an allergist to consider skin testing and desensitization may be warranted. Carrying of medical warning jewelry or wallet card is a useful and worthwhile practice.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Polycillin®, Omnipen®, Totacillin®, Amcil®, Penbretin®, Principen®	*ampicillin*
Kantrex®	*kanamycin*
Chloromycetin®	*chloramphenicol*
Cleocin®	*clindamycin*
E-mycin®, Erythrocin®, Kesso-mycin®, Ilotycin®, Robimycin®, Pediamycin®	*erythromycin*
Vancocin®	*vancomycin*
Keflin®	*cephalothin*
Garamycin®	*gentamicin*
Nebcin®	*tobramycin*
Amikacin®	*BB-K8*
Geopen®	*carbenicillin*
Pentamidine	*pentamidine isethionate*
Symmetrel®	*amantadine HCl*
Digoxin®, Lanoxin®, Davoxin®	*digoxin*
Aminophylline	*aminophylline*
Mucomyst®	*acetylcysteine*
Achromycin®, Panmycin®, Tetracyn®	*tetracycline HCl*
Valium®	*diazepam*
Thorazine®	*chlorpromazine*
Hyper-tet®	*human tetanus immune globulin*
Polymyxin B sulfate	*polymyxin B sulfate*
Mycifradin® Sulfate	*neomycin*
Viocin® Sulfate	*viomycin sulfate*
Prostigmine®	*neostigmine*
Nycillin®, Pfizerpenn®, Crysticillin®, Duracillin®	*procaine penicillin*
Epinephrine	*epinephrine*
Isoprel®	*isoproterenol*
Benadryl®	*diphenhydramine*
Solu-medrol®	*methylprednisolone*
Colistin®	*colistimethate*
Streptomycin	*streptomycin*

Addendum

A syndrome of infant botulism has recently been described. Following an unremarkable gestation and birth, the infant develops normally until

age 5 to 13 weeks. The infant then becomes constipated and weak, as manifested by less vigorous sucking from breast or bottle, weakened crying, and loss of neck and limb muscle strength. In a word, the baby appears "floppy." Prominent physical findings include ptosis, ophthalmoplegia, reduced facial expression, dysphagia, pooled oral secretions, deminished gag reflex and poor anal sphincter tone. Generalized muscle weakness is apparent; deep tendon reflexes may be deminished or absent. Fever is noted only when associated with a secondary infection, usually pneumonia. Respiratory arrest may develop. Botulinum toxin or organisms, or both, are present in the stool. The source of this infection has not yet been delineated.[104]

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