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Nonbacterial Respiratory Infections

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NONBACTERIAL respiratory infections represent a major health problem, the differential diagnosis and management of which pose a continuing problem to the physician. Annually, hundreds of thousands of days are lost from school and work by persons suffering from these infections, and several thousand fatalities occur. The nonbacterial respiratory infections comprise a spectrum of clinical syndromes, including afebrile and febrile minor undifferentiated upper respiratory tract ill-

nesses, bronchitis, croup, bronchiolitis and pneumonia (primary atypical pneumonia), some or all of which can be caused by viruses, mycoplasmas, rickettsiae and chlamydia (Table 1). These species of microorganisms are ubiquitous, occurring endemically or epidemically.

With the refinement of tissue culture technics in the early 1950s and the application of these technics to the isolation and identification of viruses, the number of viruses implicated in the etiology of acute respiratory tract infections now exceeds more than 200 (Tables 1 and 2). In adults, the influenza A viruses cause the major number of serious nonbacterial respiratory infections of the upper and lower tract. Deaths from influenza A virus infections in the United States number several thousand each year. Other myxoviruses, especially respiratory syncytial virus and the parainfluenza viruses, cause serious respiratory tract disease in infants and children, especially in infants under 1 year of age, but deaths from these infections are very few. In adults, these myxoviruses account for fewer infections, and they are less severe. A number of other virus groups cause acute respiratory tract infections in adults and children, including adenoviruses, coronaviruses and picornaviruses (enteroviruses and rhinovi-

TABLE 1.—THE PATHOGENS OF NONBACTERIAL RESPIRATORY INFECTIONS

GROUP	MAIN SUBGROUPS OR TYPES		OCCURRENCE
Viruses	Myxoviruses	Influenza	Common
		Parainfluenza	
		Respiratory syncytial	
		Rubeola	
	Adenoviruses		
	Picornaviruses	Rhinoviruses	
		Enteroviruses	
	Herpesviruses	Varicella	
	Coronaviruses		
Mycoplasmas	*Mycoplasma pneumoniae*		Common
Chlamydia	Psittacosis		Uncommon
Rickettsiae	*Coxiella burnetii* (Q fever)		Uncommon

NOTE: Although pathogenic fungi (*Histoplasma capsulatum* and *Coccidioides immitis*) may cause pneumonia with a clinical presentation not unlike a viral or mycoplasma pneumonia, they are not generally grouped with the common nonbacterial respiratory infections, and are not discussed further.

TABLE 2.—CLASSIFICATION AND CAUSATIVE ORGANISMS OF NONBACTERIAL RESPIRATORY INFECTIONS

AGE GROUP	PREDOMINANT CLINICAL SYNDROME	NONBACTERIAL PATHOGENS INVOLVED	
		MORE COMMON	LESS COMMON
Infants	Bronchiolitis	Respiratory syncytial virus, parainfluenza viruses	
	Croup	Parainfluenza viruses, respiratory syncytial virus	Influenza viruses, measles
	Pneumonia	Respiratory syncytial virus, parainfluenza viruses	Influenza viruses, adenoviruses
Children	Minor upper respiratory illness	Parainfluenza viruses, adenoviruses	Influenza viruses
	Pneumonia	Parainfluenza viruses, adenoviruses, coronaviruses, *M. pneumoniae*	Influenza viruses, adenoviruses, enteroviruses, varicella, psittacosis, Q fever
Adults	Minor upper respiratory illness	Rhinoviruses, coronaviruses	Parainfluenza viruses, enteroviruses, adenoviruses
	Febrile upper respiratory illness	Influenza viruses, parainfluenza viruses	Adenoviruses, enteroviruses
	Pneumonia (primary atypical pneumonia)	Influenza viruses, *M. pneumoniae*	Parainfluenza viruses, adenoviruses, varicella, psittacosis, Q fever

ruses), but these do so less frequently and usually with less severity than the myxoviruses.

One mycoplasma species of man, *Mycoplasma pneumoniae* (previously designated the "agent of cold agglutinin-positive primary atypical pneumonia" or the Eaton agent), causes upper and lower respiratory tract infections. Mainly it has been implicated in cold agglutinin-positive primary atypical pneumonia, but it also causes bullous myringitis and undifferentiated febrile upper respiratory tract disease. Although occurring in all age groups, *Mycoplasma pneumoniae* infections predominate in young adults. Importantly, these infections can be treated with broad-spectrum antibiotics, mainly tetracycline or erythromycin, and for this reason should be differentiated from the viral infections.

Rickettsiae and chlamydia organisms also cause pneumonia. These infections are not as common as virus and mycoplasma infections and they are more likely to be suspected in specific epidemiologic instances. *Coxiella burnetii* (Q fever) and *Chlamydia psittaci* (psittacosis) infections also can be treated effectively with broad-spectrum antibiotics, and their early diagnosis demands prompt and appropriate antibiotic treatment. Tetracycline is the usual drug of choice for infections caused by these agents.

A major obstacle in treating nonbacterial respiratory infections is the difficulty in the etiologic differentiation of these infections on clinical findings alone. Few respiratory tract diseases due to viruses, mycoplasmas or psittacosis can be etiologically recognized by a complex of symptoms and signs. However, in adult pneumonia, some differentiations can be made on the basis of epidemiologic and clinical characteristics (Table 3). In children, the fact that the same clinical syndrome can be produced by a variety of nonbacterial agents further complicates the diagnostic process (Table 4). With the introduction of new laboratory procedures, at this time available mainly in research laboratories, the diagnosis of nonbacterial respiratory infections can be accomplished more rapidly and with a greater degree of certainty than before (Table 5). Nonetheless, confirmation of specific etiologic diagnoses in nonbacterial respiratory infections usually occurs *retrospectively,* consequent to the assay of acute and convalescent

TABLE 3.—DIFFERENTIAL FEATURES OF NONBACTERIAL PNEUMONIA INFECTIONS OF ADULTS

CAUSATIVE AGENT	CLINICAL CHARACTERISTICS	EPIDEMIOLOGIC CONSIDERATIONS
Influenza A virus	High fever; prominent malaise, fatigue and myalgias; persistent cough; hemoptysis can occur	Area-wide influenza infections; usually winter months; most common cause of viral pneumonia in adults
Mycoplasma pneumoniae	Mild illness with long course; no hemoptysis; prominent cough; symptoms precede by days the radiographic findings; cold agglutinins develop; tympanitis or myringitis may complicate	Common in young adults; occurs sporadically; spreads slowly through members of household
Adenovirus	Pharyngeal erythema and tonsillar exudate; no splenomegaly	Infrequent in general population; important in captive groups—military recruits, students
Varicella	Characteristic papulovesicular rash; hemoptysis and chest pain common	History of exposure to person with varicella; area-wide outbreak of varicella; spring occurrence
Psittacosis	Severe lower respiratory tract manifestations without upper tract involvement	History of contact with infected birds
Q fever	High fluctuating fever; no rash	History of exposure to sheep, cattle or goats or ingestion of their milk

TABLE 4.—DIFFERENTIAL FEATURES OF COMMON NONBACTERIAL ILLNESSES IN CHILDREN

ILLNESS	EPIDEMIOLOGIC CONSIDERATIONS	CLINICAL CHARACTERISTICS
Pneumonia	Respiratory syncytial—usually confined to winter season, December to March; affects young infants, causing bronchiolitis as well as pneumonia	Etiology not distinguishable by clinical features
	Parainfluenza 1, 2, 3—occurs endemically	
	Influenza A and B—winter epidemics; widespread	Pneumonia usually accompanied by myalgia, malaise, inflamed mucous membranes, hoarseness
	Adenoviruses—33 types; low incidence, sporadic	Pneumonia may be severe, necrotizing type in children under 2 years, especially types 7 and 21
	Mycoplasma pneumoniae—no seasonal predominance; more likely to occur in children over 5 years of age	Usually pneumonia clears slowly; pleural effusions may occur
	Enteroviruses (ECHO and Coxsackie viruses)—occurrence in late summer, early fall; predominant type each season usually varies	Etiology not distinguishable by clinical features

Laryngotracheobronchitis (croup)	Parainfluenza 1, 2, 3—most common cause of year-round laryngotracheobronchitis in young children	Etiology not distinguishable by clinical features
	Respiratory syncytial—cause of laryngotracheobronchitis during December to March season only, especially in young infants	
	Measles—usually spring occurrence	Severe illness during exanthematous phase
Bronchiolitis	Respiratory syncytial—most common cause of bronchiolitis	Etiology not distinguishable by clinical features
	Parainfluenza 1, 2, 3—year-round occurrence in infants under 2 years of age	
Bronchitis, common cold, febrile and afebrile upper respiratory tract illness, nasopharyngitis	Many viruses—all of above, and coronaviruses and rhinoviruses	Etiology not distinguishable by clinical features

TABLE 5.—LABORATORY DIAGNOSTIC PROCEDURES FOR NONBACTERIAL RESPIRATORY INFECTIONS

METHOD AND ENDPOINT		SPECIMEN REQUIRED
Direct identification of organism in smears of exfoliated cells	Immunofluorescence with specific labeled antisera	Fresh smear of cells from nose or oropharynx
Isolation of organism from respiratory secretions	Organism growth in cell cultures or mycoplasma colonies on agar	Fresh sputum, nasal or oropharyngeal swab
Diagnostic rise in specific antibody levels during convalescence	Complement fixation, neutralization, hemagglutination-inhibition	Acute and convalescent phase sera ("paired sera")

phase sera for a rising level of antibodies to the suspected agent.

The likelihood of the development of antiviral drugs within the next few years increases the importance of etiologic diagnoses in nonbacterial respiratory infections, since such drugs may be virus specific. Selection of the appropriate drug will be based on the identification of the infecting virus before the initiation of therapy, in the same way that antibiotics now are chosen specifically in the therapy of serious bacterial infections.

Because certain viruses predominantly infect adults and cause serious respiratory infections in older individuals, and other viruses mainly cause serious lower respiratory tract infections in children, we have considered the nonbacterial virus infections by age groups. This division is not arbitrary, nor is it absolute. Some virus infections predominate in the pediatric age group but can produce respiratory tract infections in the adult. The reverse also holds true. Thus, the clinician must recognize the possibility that an individual of any age may have any one of the nonbacterial respiratory tract infections (see Table 2).

The clinical assessment of nonbacterial respiratory infections requires the utilization of epidemiologic clues, laboratory diagnostic procedures and clinical findings. Because these infections produce distinct clinical entities in children

TABLE 5 *(cont.)*—LABORATORY DIAGNOSTIC PROCEDURES FOR NONBACTERIAL RESPIRATORY INFECTIONS

RAPIDITY	USUAL AVAILABILITY	APPLICABILITY TO SUSPECTED INFECTION
Few to several hours	Research and some state health labs	Respiratory syncytial virus influenza and parainfluenza viruses
Five days to 4 weeks	State health laboratories	All viruses, chlamydia, rickettsia, *Mycoplasma pneumoniae*
Three to 4 weeks	Hospital and state health laboratories	All viruses, chlamydia, rickettsia, *Mycoplasma pneumoniae*

and adults, sometimes with important clinical differences in the two groups, those clues that might assist in their etiologic differentiation have been emphasized. Whether or not the specific etiologic agent in a nonbacterial respiratory infection can be determined—and obviously therapeutic measures demand specific etiologic diagnosis—the approach to therapy for each clinical syndrome is outlined considering the differential diagnosis. Since *Mycoplasma pneumoniae* pneumonia, Q fever and psittacosis can be treated effectively with antibiotics, etiologic recognition of these diseases becomes an important clinical consideration. Diagnosis of viral respiratory infection, however, will prevent the unnecessary use of antibiotics and alleviate the long-term complications resulting from the overusage of these drugs.

Epidemiologic Considerations

The epidemiologic characteristics of nonbacterial respiratory infections provide information useful in the differential diagnosis of these diseases. Knowledge of epidemiologic patterns of individual microorganisms can suggest likely infecting agents in individual illnesses. A definitive etiologic diagnosis requires specific laboratory tests, including virus isolation from throat swab or sputum specimens, the demonstra-

tion of viral or mycoplasma antigen in exfoliated cells of the nose or oropharnyx and/or the demonstration of a diagnostic rise in antibody levels to the infecting organism. Such studies may not be widely available in general hospital laboratories, and except for the demonstration of antigen in exfoliated cells by immunofluorescent procedures, they require several weeks before definitive answers become available. Thus, the physician faces the reality of utilizing his knowledge of epidemiologic and clinical characteristics in order to arrive at a reasonable etiologic diagnosis.

Viral and *Mycoplasma pneumoniae* infections are spread person to person by infectious droplets. The rapidity of spread in the community varies with the agent. Influenza viruses spread very rapidly and involve most susceptible persons within a few days of introduction into the community. Other viruses are communicated less quickly. *Mycoplasma pneumoniae* spreads slowly. In families, *Mycoplasma pneumoniae* eventually infects susceptible members during a period of weeks to months following the appearance of the first infection.

In adults, influenza A virus and, to a lesser extent, *Mycoplasma pneumoniae* and influenza B virus cause the predominant number of nonbacterial respiratory tract infections (see Table 2). Other viruses, psittacosis and Q fever are much less common. During epidemic periods, influenza A or B virus infections can affect the majority of susceptible adults in an exposed population, with many individuals suffering serious lower respiratory tract infections. Deaths from influenza and pneumonia reach major proportions at these times. During the epidemics of influenza A virus in the past decade in the United States, deaths from pneumonia and influenza quadrupled.

All other nonbacterial respiratory infections of the adult occur sporadically (see Table 3). Although *Mycoplasma pneumoniae* pneumonia in the adult is a serious illness, few fatalities have been recorded from this disease. Rates of *Mycoplasma pneumoniae* pneumonia in the adult population are much lower than influenza virus infections, accounting for approximately one-fifth of the nonbacterial pneumonias requiring hospitalization but as many as 20–45% of the nonbacteri-

al pneumonias in young adults, depending on the population studied. All other virus infections produce pneumonia in adults at rates considerably less than influenza and *Mycoplasma pneumoniae* infections.

In infants and children, serious lower respiratory tract infections can be caused by a number of viruses, *Mycoplasma pneumoniae,* Q fever and psittacosis (see Table 2). However, Q fever and psittacosis infections are infrequent. Among the viruses of major importance in producing acute lower respiratory tract disease are the parainfluenza viruses, especially parainfluenza types 1 and 3, respiratory syncytial virus, adenoviruses, influenza A virus and coronaviruses. The parainfluenza viruses occur endemically and are associated with serious infections throughout the year (see Table 3). Outbreaks of respiratory syncytial virus occur annually sometime between December and April and produce widespread infection of susceptible infants and children under 1 year of age. Influenza A virus infections occur epidemically every 2–3 years and, although they produce serious lower respiratory tract infections in children, the pneumonia rates in children for these infections are lower than in the adult. Influenza viruses also cause bronchiolitis, laryngotracheobronchitis and acute bronchitis. Adenovirus infections occur sporadically and coronavirus infections occur as limited outbreaks annually or less often. *Mycoplasma pneumoniae* infections are uncommon in infants, and in children they are much less frequent than are infections with parainfluenza, respiratory syncytial and influenza viruses.

The major nonbacterial respiratory infections of the lower respiratory tract include pneumonia in adults and pneumonia, bronchiolitis and croup in infants and children. Upper respiratory tract infections include acute undifferentiated minor respiratory illness (the common cold), influenza illnesses, undifferentiated febrile upper respiratory tract illnesses and a "pertussis-like" viral coryza in children. Croup in younger children is subdifferentiated into the infraglottic type, which occurs in children less than 2–3 years of age, and the supraglottic type, which is found more often in older children. The etiologic agents involved in these two illnesses are different; infraglottic croup in young children more commonly is caused

by viruses and supraglottic croup, especially when it occurs with epiglottitis, commonly is caused by *Hemophilus influenzae.*

Nonbacterial Respiratory Infections of Children

The general criteria for a clinical classification of the nonbacterial respiratory syndromes include: for pneumonia, symptoms of coryza and respiratory distress and the finding of moist rales or decreased breath sounds; and the demonstration of an infiltrate by radiographic examination. Bronchiolitis can be differentiated on the basis of a mild upper respiratory infection with progressive dyspnea, tachypnea, suprasternal and subcostal retractions, expiratory wheèzes and scattered rales and radiographic findings of air trapping; croup or laryngotracheobronchitis includes a harsh "croupy" (bark-like) cough, stridor and signs suggesting inspiratory obstruction. Bronchitis is characterized by a "brassy" (harsh) cough, congestion and rhonchi on auscultation of the chest. The roentgenogram usually is negative. Upper respiratory tract syndromes lack the severity of fever, productive cough, respiratory distress or the presence of such constitutional manifestations as malaise, fatigue and anorexia.

PNEUMONIA

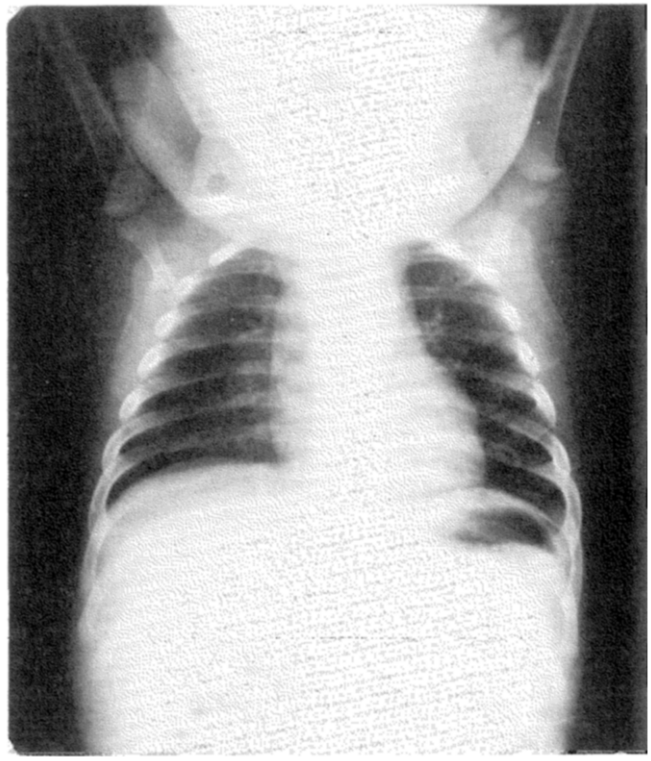
Evidence of a viral etiology can be detected in more than half of children with a diagnosis of pneumonia (see Table 4). The predominant agents include, in descending order: the parainfluenza viruses types 3, 2 and 1; respiratory syncytial virus; influenza A viruses; adenoviruses, *Mycoplasma pneumoniae* and coronaviruses. Mixed viral and bacterial infections occur infrequently; when these infections are suspected, antibiotic therapy is indicated.

The clinical differentiation of viral pneumonia from bacterial pneumonia is difficult and extremely tenuous in many cases. Insidious onset with upper respiratory symptoms preceding an increase in temperature and dyspnea usually suggests a viral etiology. Abrupt onset of symptoms with high fever is characteristic of a bacterial pneumonia. Diffuse infil-

trates without pleural fluid are seen commonly in roentgenograms of patients with viral pneumonia (Figs. 1 and 2). *Mycoplasma pneumoniae* may also cause pleural effusion. The low incidence of bacteremia in children is consistent with the fact that most pneumonias of children are viral in nature.

The child with acute lower respiratory tract infection presents a difficult diagnostic and therapeutic problem (see Table 3). Except for lung puncture, no effective or quick methods exist to ascertain the specific etiology of lung disease; lung puncture is a highly selective procedure. Most pediatricians rely on oropharyngeal swab specimens or blood cultures for clues to the etiology of these illnesses, but oropharyngeal

Fig. 1.—Parainfluenza 3 virus pneumonia (in a 4-month-old child). Bilateral diffuse pneumonia.



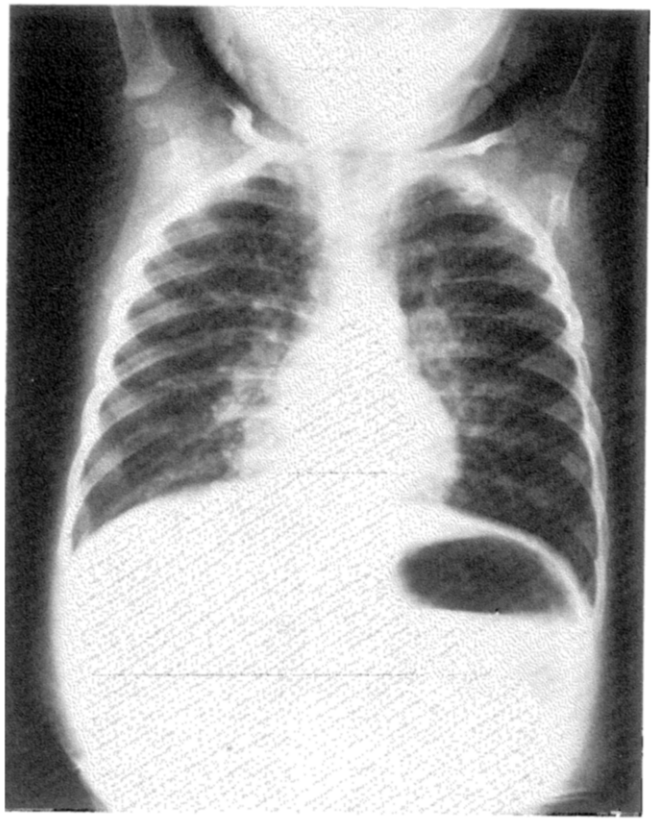


Fig. 2.—Respiratory syncytial virus pneumonia (in a 9-month-old child). Bilateral perihilar pneumonia with diffuse interstitial infiltrates.

swabs for bacteria correlate poorly with the etiologic organisms in lower respiratory infections, and bacteremias in children are uncommon.

The therapy of viral pneumonia in children is supportive and aimed at alleviating the symptoms and distress of the disease. Antibiotics are not recommended for uncomplicated viral pneumonia in children. However, when secondary infection develops or is suspected, usually because of hyperpyrexia and leukocytosis, antibiotics may be used. Penicillin, ampicillin, erythromycin and the cephalosporins are the most com-

monly selected. For *Mycoplasma pneumoniae* pneumonia, the treatment is tetracycline or erythromycin.

Bronchiolitis

Bronchiolitis is uniquely a pediatric disease, usually observed during the winter months in infants under 6 months of age. The basic pathology is an inflammatory obstruction of the bronchioles with air trapping. The disease is characterized by a history of upper respiratory tract symptoms, including cough, rhinitis and a low-grade fever, lasting 3–4 days, with progressive dyspnea, which often is the most impressive initial sign. Physical examination usually reveals hyperemic mucous membranes, but the significant findings are in the chest, including rapid but shallow respiration, increased resonance and inspiratory and expiratory wheezes, which may be heard along with occasional scattered fine rales. Hyperaerated lungs secondary to air trapping may push the diaphragm down, allowing palpation of the liver.

During the winter months, this disease almost invariably is due to respiratory syncytial virus infection, which is epidemic. Respiratory syncytial virus causes an increase in other respiratory tract infections, such as mild upper respiratory tract illnesses, pneumonia and laryngotracheobronchitis. Total white blood cell and differential counts usually are normal or not significantly different from the normal; the temperature usually is not greater than 102 F.

The chest roentgenogram in bronchiolitis shows evidence of air trapping with radiolucency, widened spaces between the ribs and a flat diaphragm (Figs. 3 and 4). Scattered infiltrates and areas of atelectasis occur infrequently.

Therapy for bronchiolitis is directed toward relieving obstruction and bronchial spasm. Ultrasonic mist may be used for this purpose. Correcting hypoxia with oxygen, 40% or more, vigilance against bacterial and cardiac complications and antibiotic treatment only when secondary infections are apparent or suspected constitute the main thrust of therapy in bronchiolitis. Intravenous fluids are given to maintain hydration and prevent aspiration in those infants who are distressed and would be at risk with oral feedings. Bronchodilators usually are ineffective.

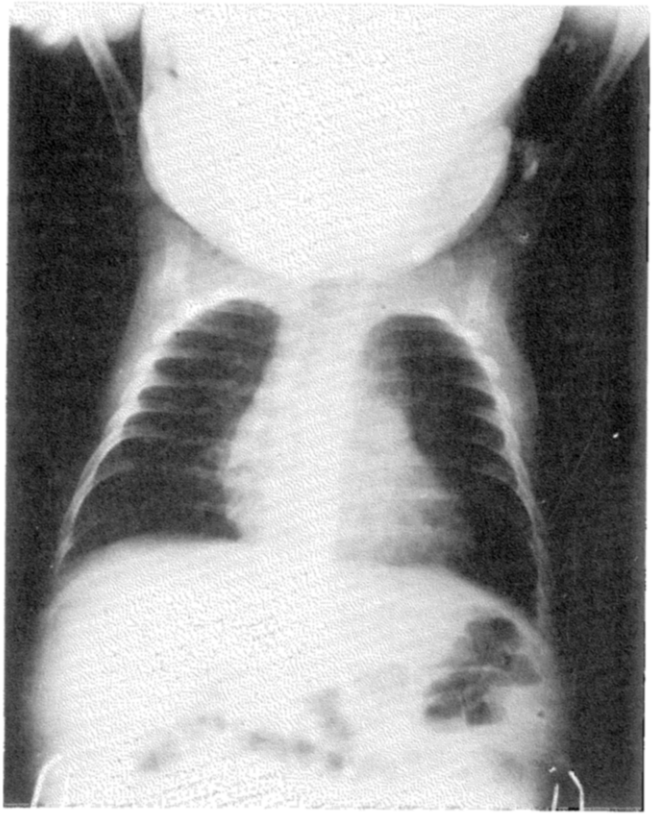


Fig. 3.—Respiratory syncytial virus bronchiolitis (in a 2-month-old child). Note air trapping, hyperaerated lung fields and flattened diaphragm.

Administration of steroids in cases of bronchiolitis has not proved beneficial except in recurrent attacks, when an allergic diathesis may be involved in the underlying etiology. A tracheostomy is done only as a last resort and rarely should be necessary. In the differential diagnosis of bronchiolitis, consideration must be given to foreign bodies, the milk allergy syndrome of Heiner, myocarditis, congestive heart failure, asthma and certain intoxicants (e.g., organophosphates).

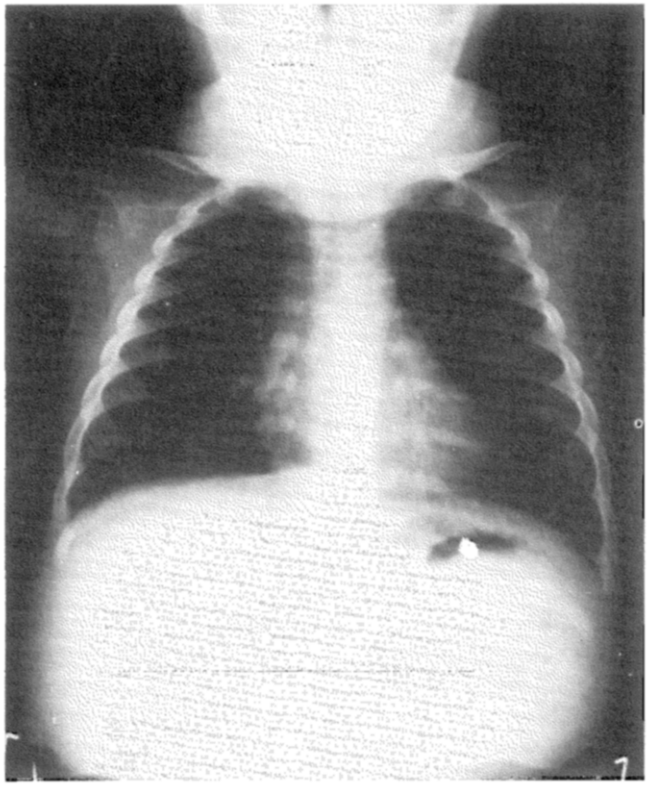


Fig. 4.—Respiratory syncytial virus bronchiolitis (in a 5-month-old child). Note air trapping, hyperaerated lung fields and flattened diaphragm.

LARYNGOTRACHEOBRONCHITIS

Laryngotracheobronchial syndrome (laryngitis, tracheitis, croup with epiglottitis and viral croup) reflects varying degrees of airway obstruction, usually caused by inflammatory edema, spasm and exudate, and localized anatomically either above or below the glottis. This disease is seen commonly in the winter months and predominates in males. On physical examination, respiratory stridor and retraction with hoarseness and barking cough predominate.

Two distinct forms of this disease are recognized: (1) acute supraglottic laryngitis and (2) acute infraglottic (subglottic) laryngitis. Supraglottic laryngitis is much more common in the older child, 3–6 years of age, and usually is accompanied by infection and swelling of the epiglottis, which can rapidly obstruct and cause severe inspiratory distress, suffocation and death. The supraglottic type usually is caused by *Hemophilus influenzae* B, and ampicillin is the usual drug of choice. It should be noted that croup in the younger age group (6 months to 3 years) is caused most often by viral infections. Viral croup rarely is obstructive and usually runs a milder course than the supraglottic croup with epiglottitis. It may, however, be recurrent. The major agent associated with croup in the infant is parainfluenza 3 virus. The chest roentgenogram is not pathognomonic in the viral croup, where it usually is normal, but it helps to eliminate the possibility of an aspirated foreign body.

Therapy of viral croup consists of basically supportive measures and the exclusion of an allergic bronchitis or the ingestion or aspiration of a foreign body as a possible cause of the clinical syndrome. Vigilance against obstruction and maintenance of hydration are essential. Cultures must be taken to rule out a bacterial etiology, specifically *H. influenzae* B and *C. diphtheriae*. If diphtheria is suspected, antitoxin and penicillin should be administered immediately; with the isolation of *H. influenzae*, ampicillin is indicated. A croupette or therapy with cool humidity oxygen mist is invaluable in relieving dyspnea, stridor and hypoxia. Atropine should not be given. Mild sedation may be beneficial (chloral hydrate 10–15 mg/kg every 6–8 hours) but care should be exercised in its administration. Ampicillin 200–300 mg/kg intravenously per day is indicated with epiglottitis or when secondary infection is suspected. Intermittent positive-pressure breathing (IPPB) treatments with aerosolized racemic epinephrine (Vaponefrin) (2.5%) diluted in normal saline and repeated every 30 minutes may be of great benefit. Tracheostomy may be lifesaving in croup with epiglottitis. In controlled studies, steroids have not been shown to be effective in relieving distress in viral croup, although they are used widely.

Bronchitis

Upper respiratory tract infections such as coryza, bronchitis and pharyngitis, with or without rhinitis, are responsible for more illnesses in children than any other cause. Viruses invade the passages of the upper respiratory tract and extend to the lower air passages. The resulting bronchitis frequently is associated with laryngitis, low-grade fever and coarse breath sounds or rhonchi. The chest roentgenogram usually is normal or shows perihilar infiltrates. The total leukocyte count is normal. Therapy consists of expectorants, antitussives, decongestants and antihistamines. When secondary infection is suspected, antibiotics also may be important in the treatment of bronchitis.

Recurrent Viral Respiratory Infections in Children

The child with recurrent lower respiratory tract infection presents a special diagnostic challenge to the physician. Either the child is experiencing multiple infections with different microorganisms or has an unrecognized chronic illness with repeated exacerbations. The essential causes of recurrent nonbacterial respiratory infections can include allergic, environmental or familial factors, immune deficiencies, congenital abnormalities of the tracheobronchial and esophageal pathways and innate lung disease, such as asthma, cystic fibrosis, pulmonary hemosiderosis and bronchopulmonary dysplasia. The search for an underlying disease not only must include the investigation of the specific nonbacterial respiratory tract infection by means of laboratory tests aimed at isolation of the organism or determination of antibody responses but also must encompass the tests necessary to search for one of the other underlying causes.

In this respect, the following discussion highlights some recommended procedures for investigating the nature of the predisposing underlying or chronic illnesses. A detailed history can uncover information on possible allergic, familial and environmental factors that may play a role in recurrence or chronicity. Day care and nursery school children are particularly prone to recurrent viral illnesses because of their fre-

quent exposure to and repeated contact with infected playmates.

An underlying allergic diathesis probably represents the most common cause of recurrent lower respiratory tract illnesses. Children who have allergic rhinitis and persistent or intermittent wheezing, and come from a family with a history of allergy, seem to be more susceptible to recurrent viral infections and involve a significant percentage of office visits. The nasal smear for eosinophils and scratch tests using especially inhalant antigens may be helpful in determing antigenic sensitivities.

The possibility of an immune disorder or hypogammaglobulinemia may be suggested by chronic gastroenteritis, persistent oral moniliasis, a significant leukopenia (usually 1500/mm^3) involving small lymphocytes or a thrombocytopenia. Chest roentgenograms should be re-reviewed to evalutate the thymic shadow and lymphoid tissue; the absence of a thymic shadow suggests an immune disease. Quantitative assay of immunoglobulins may indicate selective immune deficiencies. Delayed maturation of antibody or transient hypogammaglobulinemia can be associated with recurrent infections in children under 3 years of age. Skin tests (including Mantoux, Schick and *C. albicans*) can be applied presumptively to test the patient for competence of delayed hypersensitivity. The definitive tests for delayed hypersensitivity (or cellular immunity) are the dinitrofluorobenzene (DNFB) skin test and in-vitro lymphocyte stimulation.

An abnormal cardiac silhouette and electrocardiogram suggest congenital heart disease. A barium swallow should be performed to explore the presence of vascular and tracheoesophageal anomalies. When an H type fistula* is suspected, the diagnosis must be made by bronchoesophagoscopy and cineradiography. In selected cases, lung puncture and biopsy may be considered.

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*An H type fistula is a rare type of congenital abnormality of the esophagus. In this defect there is no atresia of the esophagus; it is complete. There is a connection between the esophagus and the trachea resembling the letter H.

Nonbacterial Respiratory Infections of Adults

Upper Respiratory Tract Illnesses

Nonbacterial upper respiratory tract illnesses of adults include the several syndromes designated as common cold, minor or undifferentiated upper respiratory infection and febrile upper respiratory disease (especially influenza or influenza-like disease). For this discussion, nonbacterial upper respiratory tract illnesses are considered broadly as either afebrile or febrile. The major number of febrile upper respiratory tract illnesses usually are caused by influenza virus, with myxoviruses, coronaviruses and adenoviruses accounting for a small proportion of these illnesses. Afebrile upper respiratory tract illnesses can be caused by most viruses capable of infecting the respiratory tract, and especially the rhinoviruses, myxoviruses, enteroviruses, coronaviruses and adenoviruses. *Mycoplasma pneumoniae* has been associated with these syndromes. Importantly, etiologic differentiation of upper respiratory tract illnesses cannot be accomplished on the basis of clinical findings alone.

Afebrile upper respiratory tract illnesses are characterized by nasal discharge or nasal obstruction in all patients and nonproductive cough in approximately two-thirds of patients. Less often, a chilly sensation and myalgias may occur. In febrile upper respiratory tract illnesses, fever and chills predominate, with myalgias, fatigue and muscle aches occurring frequently. Nasal symptoms occur in most patients, and some patients experience sore throat or hoarseness as well.

These illnesses are self-limiting and of short duration. The treatment of nonbacterial upper respiratory tract illness consists of supportive measures aimed at minimizing the symptoms of the infection.

Pneumonia (Primary Atypical Pneumonia)

Historically, the term primary atypical pneumonia was first used in the early 1940s to connote acute lower respiratory tract infection of a nonbacterial etiology. These illnesses were "atypical" because they were not "typical" bacterial

(pneumococcal) pneumonias. At that time, implicit in the use of the term primary atypical pneumonia was the consideration that one or more specific, but yet undiscovered, microorganisms caused these illnesses. Now, primary atypical pneumonia comprises a group of pneumonia illnesses whose etiology includes a number of different microorganisms, particularly *Mycoplasma pneumoniae* and viruses (but not bacteria).

Mycoplasma pneumoniae (earlier designated the agent of primary atypical pneumonia or the Eaton agent) was recognized as the etiologic agent of cold agglutinin-positive primary atypical pneumonia only in the late 1950s. Mycoplasmas are the smallest microorganisms capable of growth on cell-free medium. They are 150–250 millimicrons in size, pleomorphic in shape, contain both DNA and RNA and lack a rigid cell wall but possess a triple-layered outer membrane. They replicate both intracellularly and extracellularly. *Mycoplasma pneumoniae* produces a hemolysin that is a peroxide. Unlike viruses, it is sensitive to treatment with tetracyclines and erythromycin. We now know that the equivocal but suggestive results of double-blind antibiotic treatment studies of primary atypical pneumonia conducted during the 1950s were dependent on the proportion of *Mycoplasma pneumoniae* infections in the study group and their distribution between the treatment and placebo groups. The recognition of *Mycoplasma pneumoniae* as the cause of cold agglutinin-positive primary atypical pneumonia and the characterization of this disease now permits its specific delineation and it is appropriately referred to as *Mycoplasma pneumoniae* pneumonia. In addition, a number of viruses have been shown to cause pneumonia, especially the myxoviruses and adenoviruses, and these should also be designated by their specific etiologic names. Less and less use is made of the term primary atypical pneumonia when an etiologic agent can be identified.

Among the causes of nonbacterial pneumonia in the adult, influenza A virus and *Mycoplasma pneumoniae* infections predominate (see Table 3). Other viruses that produce pneumonia in adults include the adenoviruses; parainfluenza viruses and respiratory syncytial virus do so infrequently. Varicella, psittacosis and Q fever are uncommon causes of pneumonia in adults.

Few clinical features allow the differentiation of the etiolo-

gy of nonbacterial pneumonia in adults without recourse to laboratory diagnostic procedures. However, the occurrence of certain clinical and epidemiologic findings may suggest to the physician the specific cause of the disease (see Table 3). Confirmation of the identity of the infecting organism must be obtained through laboratory diagnosis.

MYCOPLASMA PNEUMONIAE PNEUMONIA.—In *Mycoplasma pneumoniae* pneumonia, cough is the most frequent initial finding, usually nonproductive during the first few days of illness and then becoming productive. Hemoptysis rarely occurs; as an early and predominant finding, hemoptysis suggests an etiologic agent other than *Mycoplasma pneumoniae*. Headache, chills, malaise, rhinorrhea, chest pain and generalized muscle aches occur in more than half of patients. Nearly all patients develop fever. Rales, which may develop only after the first few days of illness, occur in at least four-fifths of patients. Patients with *Mycoplasma pneumoniae* pneumonia uniquely may develop a bullous myringitis or a tympanitis. In untreated cases, fever usually lasts 1–2 weeks, and rales, cough, malaise and fatigue and radiographic abnormalities persist for 2–3 weeks. A small number of patients experience fever lasting more than 4 weeks and abnormal radiographic findings lasting as long as 4 months. In rare instances, a residual pleural abnormality can be found on the chest roentgenogram. Leukocytosis develops in about one-sixth of cases and the sedimentation rate is elevated in about one-fourth of cases. Bacterial superinfection rarely occurs in *Mycoplasma pneumoniae* pneumonia.

In *Mycoplasma pneumoniae* pneumonia, no specific radiographic pattern prevails. Most often, the pneumonic infiltrate is unilateral, located in the lower lobes (Figs. 5 and 6). About one-fifth of patients have bilateral involvement (Fig. 7). The infiltrative process in *Mycoplasma pneumoniae* pneumonia appears patchy or fluffy. Characteristically, the infiltrate shows punctate mottling. The infiltrates are bronchiolar or peribronchiolar and generally follow the course of the bronchovascular markings. Lobar involvement is distinctly unusual. A few patients develop infiltrates in the middle and upper lobes, and this radiographic picture must be differentiated from acute pulmonary tuberculosis. Pleural effusions occur in *Mycoplasma pneumoniae* pneumonia perhaps in no

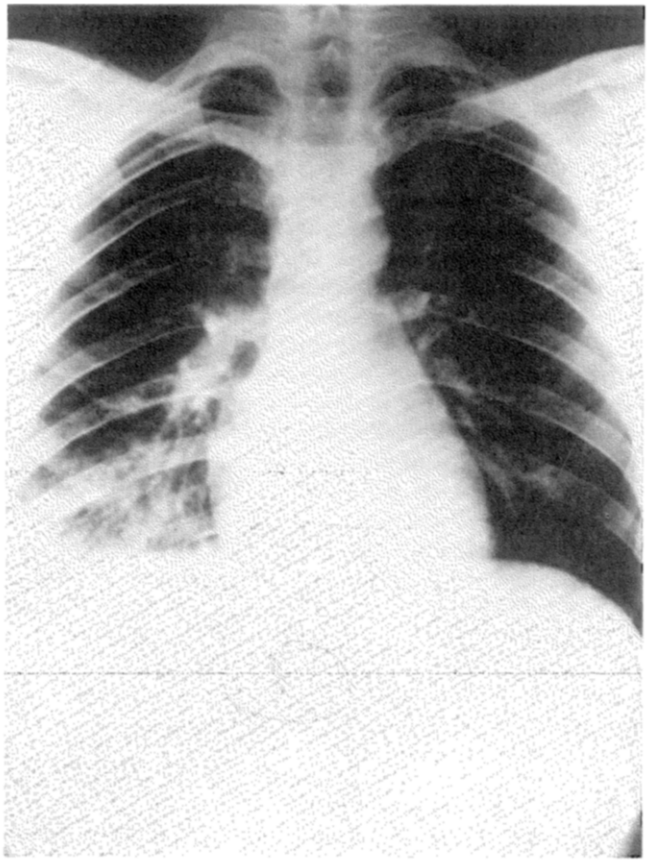

Fig. 5.—*Mycoplasma pneumoniae* pneumonia. The infiltrate extends from the right hilum to the right lower lobe.

more than 20% of patients, less often in adults than in children. It may be difficult to obtain fluid at thoracentesis from small collections of pleural fluid. The fluid is serous with a high protein content, approximately 4 gm/100 ml.

A very small number of patients with *Mycoplasma pneumoniae* pneumonia, usually adolescents, may develop central nervous system complications involving the cerebrum, the cerebellum, spinal cord or nerve roots; meningitis, encephali-

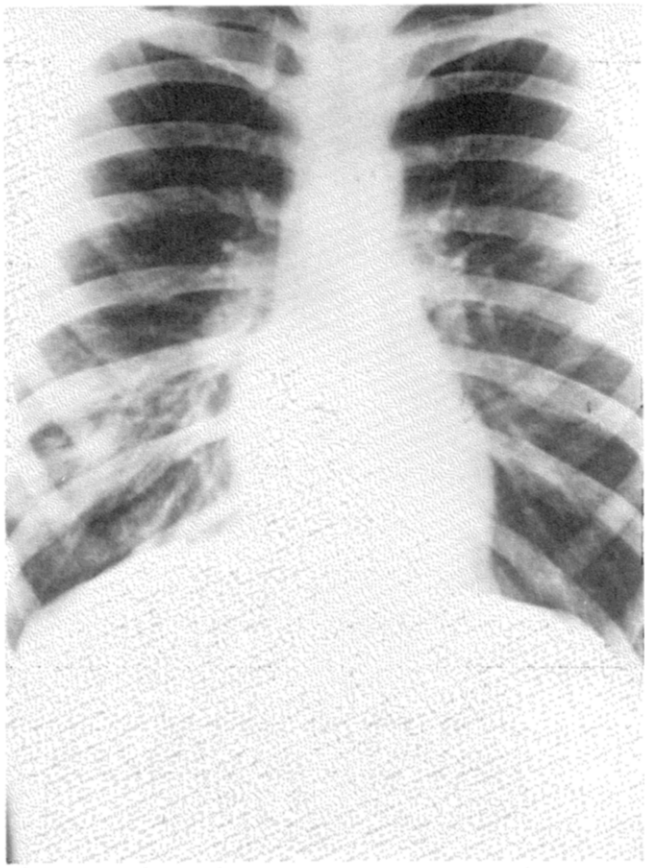

Fig. 6.—*Mycoplasma pneumoniae* pneumonia. The infiltrate process is patchy, involving the right middle lung field.

tis, cerebellar ataxia and psychosis have been reported also. Residual neurologic abnormalities occur in a small but significant number of patients. Since the appearance of such central nervous system abnormalities in viral pneumonia are rare, the findings should encourage a search for *Mycoplasma pneumoniae* infection.

The development of cold agglutinins to a titer exceeding 1:40 during the course of a nonbacterial pneumonia is pre-

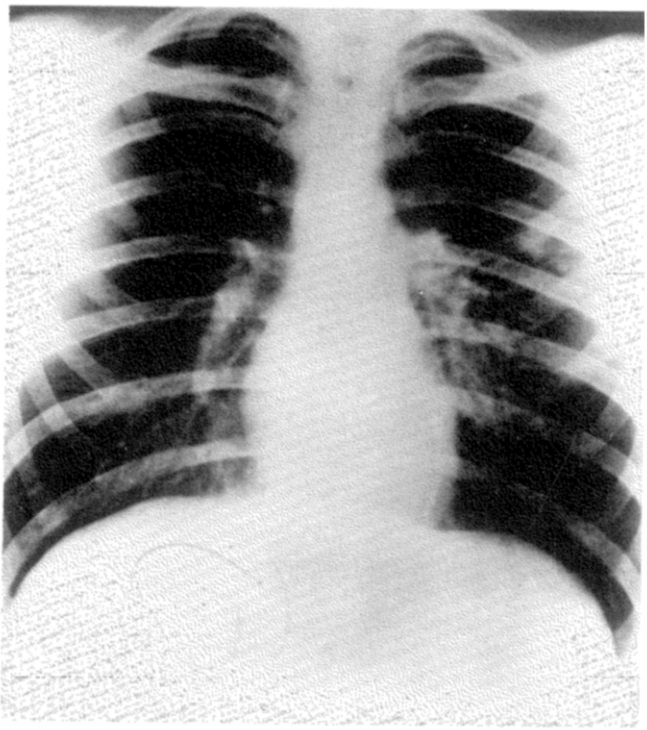

Fig. 7.—*Mycoplasma pneumoniae* pneumonia. Bilateral infiltrate.

sumptive evidence of *Mycoplasma pneumoniae* infection. Cold agglutinins appear more frequently in the severely ill patient but, over-all, only about half of individuals with *Mycoplasma pneumoniae* pneumonia develop cold agglutinins. Specific *Mycoplasma pneumoniae* antibody, measured by complement fixation, metabolic inhibition or immunofluorescence, develops during convalescence in nearly all patients with this infection (see Table 5). No cross relationship exists between specific *Mycoplasma pneumoniae* antibody and cold agglutinin antibody. In the absence of the availability of a test to determine specific *Mycoplasma pneumoniae* antibody, the demonstration of high titers of cold agglutinins provides strong presumptive evidence of infection with *My-*

coplasma pneumoniae and justifies the initiation of proper antibiotic treatment.

Cold agglutinins (globulins of the IgM class) formed during *Mycoplasma pneumoniae* infections have anti-I specificity for I-positive erythrocytes, perhaps because this organism contains antigens that cross react with erythrocytes. Some patients with high levels of cold agglutinins develop hemolysis and anemia during the course of *Mycoplasma pneumoniae* pneumonia. Prompt administration of antibiotics will effectively treat the pneumonia and should result in reversal of the anemia.

Treatment of *Mycoplasma pneumoniae* pneumonia includes, in addition to specific antimicrobial therapy, bed rest, adequate diet, liquids, salicylates and antitussive medication and bronchodilator drugs as required for respiratory distress. Tetracycline 2 gm daily in divided doses or erythromycin 1 – 2 gm daily in divided doses for about 10 days will effectively treat the disease, lessen the severity of symptoms and signs and shorten the course of illness. Antibiotics should be given until the disease abates. Also effective in the treatment of this disease is one of the tetracycline analogues (oxytetracycline, chlortetracycline or demethylchlortetracycline) in appropriate doses. Recurrent pneumonias with *Mycoplasma pneumoniae* infection occur infrequently and respond to retreatment. Although antimicrobial therapy lessens the severity of the disease and shortens the illness, it does not immediately eradicate the organism from the respiratory tract, and patients on therapy still may shed the organism in their respiratory secretions.

INFLUENZA VIRUS PNEUMONIA.—Influenza A virus pneumonia, the most common cause of pneumonia in adults and the most frequent cause of hospitalization in nonbacterial pneumonias, can present as a primary influenzal pneumonia in about one-fourth of the cases in influenza infection. Primary influenzal pneumonia occurs predominantly in pregnant women and patients with rheumatic heart disease. Other patients with influenza more frequently develop complicating bacterial superinfection and pneumonia. Influenza B virus infrequently causes pneumonia. Primary influenzal pneumonia is characterized by involvement of the lower respiratory tract

during a typical influenzal illness. High fever develops that does not readily abate, and cough, tachypnea and dyspnea are prominent. Cough is paroxysmal and may be nonproductive at the beginning of the illness. Headache, sore throat, prominent muscle aches, fatigue and anorexia, signs of bronchitis and occasionally hemoptysis characterize influenzal virus pneumonia. Rales appear in most patients, but in the absence of bacterial superinfection, physical signs of consolidation are unusual. On radiographic examination, the infiltrates appear diffuse and usually are bilateral. In patients with complicating diseases such as rheumatic heart disease or chronic lung disease, the pneumonia is rapidly progressive and the case fatality rate is high. Signs of focal consolidation develop in the presence of bacterial superinfection, usually by pneumococci, staphylococci or *Hemophilus influenzae*. A leukocytosis occurs in primary influenzal pneumonia, usually ranging between 12,000 and 18,000 cells/mm^3, whether or not the illness is complicated by bacterial infection.

Patients with primary influenzal pneumonia should be treated with general supportive measures, including bed rest, adequate diet, liquids, salicylates and oxygen nasally or by mask or by IPPB devices when respiratory distress and dyspnea predominate. Unless bacterial superinfection intervenes in influenza virus pneumonia, no antibiotic therapy is required. Superinfection with bacteria demands rapid initiation of antibiotic therapy directed at the infecting organism.

Amantadine is effective only in the prophylaxis of influenza A virus infection (see section on Virus Vaccines and Viral Chemotherapy). Once signs and symptoms of infection develop, this drug is ineffective.

ADENOVIRUS PNEUMONIA.—Adenovirus pneumonias occur infrequently in adults but are found more often among special population groups, especially military recruits. In military recruits, adenoviruses often produce pneumonia as well as severe febrile upper respiratory tract disease. Fatalities among adults are extremely rare, but they have been reported in selected sharp outbreaks of the disease among children. The common infecting types in young adults are types 3, 4 and 7, which contrast with the usual childhood infections of types 1, 2, 3, 5, 6 and 7. Adenovirus pneumonia is character-

ized by cough, chills, sore throat, rhinorrhea, less often headache and generalized muscle aches. Fever predominates and about two-thirds of patients develop rales. Tonsillar exudate develops in about one-fourth of patients and suggests adenovirus infection. Pharyngeal erythema occurs in about one-fifth of patients.

Radiographic infiltrates usually are unilateral and confined to the lower lobes; only frequently are they bilateral and/or involve the hilar regions. The characteristic features of the infiltrates resemble those in *Mycoplasma pneumoniae* pneumonia. Bronchiolar or peribronchiolar patterns predominate and the infiltrates are fluffy or patchy. Bacterial superinfection in adenovirus pneumonia occurs rarely. The treatment of adenovirus pneumonia includes general supportive measures aimed at relieving the distress and fever of the illness and alleviating respiratory distress.

OTHER NONBACTERIAL PNEUMONIAS.—Viral pneumonias can be associated with parainfluenza virus, respiratory syncytial virus, enterovirus, measles or varicella infections, but these cases are uncommon. The presence of the pathognomonic findings of measles or chickenpox permits etiologic recognition. Psittacosis and Q fever also are infrequent causes of nonbacterial pneumonia and can be treated effectively with antibiotics.

Varicella pneumonia develops within the first week after the rash of chickenpox appears, characterized by cough and pleuritic chest pain, hemoptysis, fever and respiratory distress. The hemoptysis can last several days. By contrast, pleuritic chest pain and hemoptysis are infrequent or rare in other viral pneumonias and in *Mycoplasma pneumoniae* pneumonia. Physical findings frequently belie the severity of illness in varicella pneumonia. Few adventitious sounds (rhonchi and wheezes) are found. The chest roentgenogram, however, shows a bilateral infiltration, at first nodular but then developing a definite acinar pattern with hilar adenopathy. Usually about one-third of patients have a leukocytosis. During convalescence, complement-fixing antibodies for varicella virus develop, and serologic diagnosis of this infection can be made by the detection of a fourfold or greater rise in antibody in paired sera. Deaths from varicella pneumonia

approach 30% of cases, usually caused by respiratory insufficiency.

Treatment of varicella pneumonia includes supportive measures and, in the immune incompetent patient, zoster immune globulin (ZIG) may be given as a single 10-ml intramuscular injection (see section on Virus Vaccines and Viral Chemotherapy). Adrenal corticosteroids, although ordinarily not indicated in the treatment of varicella pneumonia, may be used in the most severe cases complicated by shock.

Psittacosis complicated by pneumonia is acquired by man through contact with infected birds. It is an occupational hazard of bird handlers in pet shops or in industry. The appearance of symptoms and signs ensues within 1–2 weeks after exposure and includes high fever, headache, chilly sensations, sore throat, productive cough, photophobia, nausea and vomiting. Sputum may be tinged with blood. The pneumonia is diffuse and interstitial; fine rales may be detected by auscultation. Hepatosplenomegaly occurs infrequently. Psittacosis pneumonia persists for between 1 and 3 weeks. The treatment of choice is tetracycline, 2–4 gm daily in divided doses administered until 1 week after abatement of the illness. During convalescence, specific complement-fixing antibodies develop to *Chlamydia psittaci,* and fourfold or greater rises in antibody are diagnostic of this infection (see Table 5). A presumptive specific diagnosis can be made when only a single serum is available by detection of a titer of 1:16 or greater. Although the organism can be isolated from the sputum or blood during the acute phase of illness, this agent can easily be transmitted to laboratory workers unless rigid containment procedures are used. In the routine diagnostic examination of nonbacterial pneumonia, attempts to isolate *Chlamydia psittaci,* especially by inexperienced personnel, are unwarranted.

Q fever with pneumonia is contracted by ingestion of contaminated milk or exposures to aerosols or infected feces from sheep, goats and cattle. Although these animals become infected with *Coxiella burnetii* by tick bite, man does not. Signs and symptoms appear abruptly and characteristically include severe headache, fever, chills, malaise and myalgias, but no rash. Pneumonia, usually unilateral, occurs in approximately one-half of cases. Hepatosplenomegaly frequently develops. Q fever usually lasts several weeks, and nearly all

patients recover without incident. A serologic diagnosis of infection can be made by the detection of a fourfold or greater rise in complement-fixing antibody during convalescence. Q fever fails to react in the Weil-Felix test with *Proteus vulgaris*. As with psittacosis, isolation of the organisms should not be attempted except in unusual circumstances, since it is highly contagious. Tetracycline, 2–4 gm daily in divided doses, is the treatment of choice, continued until 5 days after the illness resolves.

Immunologic Considerations

The major defense mechanism in nonbacterial infections is the IgA secretory antibody system. IgA, one of four major proteins found in nasal secretions, along with albumin, small amounts of IgG (gamma globulin) and siderophilin, is the most significant component of nasal secretions and primarily functions in local immunity. Secretory IgA has a sedimentation coefficient of 11S and additional antigenic characteristics that differentiate it from circulating (serum) IgA, which is 7S. Structurally, secretory IgA is composed of 4 H chains and 4 L chains plus a unique component designated as transport piece. The transport piece plays a role in the passage of IgA through cells to their surfaces, where the secretory IgA can act. Secretory IgA is found in the secretions from the upper and lower respiratory tract, parotid saliva, colostrum and tears. The defense function of secretory IgA is suggested by its major production following topical immunization (intranasal or pharyngeal instillation) of antigen. In contrast, little or no response in secretory IgA antibody occurs in response to immunization by the systemic route. Most IgA appearing in the respiratory tract secretions is synthesized locally by plasma cells in the adjacent tissues. Diminished host resistance may be related to a selective IgA deficiency; affected patients may have recurrent lower respiratory tract infections, allergic syndromes or an autoimmune disorder, or may appear to be healthy adults. A combined deficiency in IgA and cell-mediated immunity contributes to the development of severe respiratory tract infections.

Hypogammaglobulinemia of infancy is a self-limited disor-

der characterized by delayed maturation of IgG synthesis. After the normal decline in transplacental antibodies during the first months of life there is a significant delay in gamma globulin synthesis. Usually, normal levels of immunoglobulins are attained by 2–4 years of age. Respiratory tract infections are common during this period and immunoglobulin levels are low, usually below 400 mg/100 ml. Gamma globulin may be given to affected infants with severe symptoms, which, in addition to recurrent respiratory illness, include failure to thrive and intermittent diarrhea.

Other miscellaneous dysgammaglobulinemias may also be associated with increased susceptibility to infection. Commonly, the pattern of immunoglobulins shows absence of circulating IgA and IgM and low levels of IgG. Alternatively, in another type of dysgammaglobulinemia, IgM is increased. A total immunoglobulin level exceeding 600 mg/100 ml detected by quantitative radial immunodiffusion determinations excludes an immunoglobulin deficiency syndrome. In general, the recognition of hypogammaglobulinemia in children is signaled by total immunoglobulin levels less than 400 mg/100 ml or IgG levels less than 200 mg/100 ml.

Gamma globulin therapy remains controversial and should be considered only for IgG-deficient patients. Commercial gamma globulin is derived from pooled sera and contains almost exclusively IgG. The initial dose is 1.8 ml/kg intramuscularly followed by a maintenance dose of 0.6 ml/kg given every 3 or 4 weeks for 12–18 months.

Laboratory Procedures

Although certain laboratory tests used in the diagnosis of nonbacterial respiratory infections can provide specific information quite rapidly, the major limitation of most procedures is that they require days to weeks before definitive answers, either positive or negative, are available (see Table 5). Moreover, at present, few tests may be done in small hospitals or state health department laboratories; the newer tests are available mainly through medical centers and their research facilities.

Three types of laboratory tests have been developed for the

diagnosis of nonbacterial respiratory infections: (1) immunofluorescent identification of viral antigen in exfoliated cells of the respiratory tract, (2) isolation (and identification) of the infecting microorganism from respiratory secretions and (3) demonstration of rising antibodies between acute and convalescent serum specimens. Only the first test, the immunofluorescent identification of viral antigen in respiratory tract cells, provides a rapid means of specific diagnosis. Depending on the infecting agent, isolation procedures can require from 5 days to 3 weeks, if the tests are positive at all. Negative tests require at least 4 weeks before a final report is returned. Of necessity, antibody studies are done retrospectively, since they require a second serum specimen obtained during convalescence. Single serum specimens cannot be used, except in unusual circumstances. For example, a single high titer of cold agglutinins obtained in the early phase of a pneumonic illness provides presumptive but not definitive evidence of *Mycoplasma pneumoniae* infection. Nonetheless, acute and convalescent serum specimens must be tested in parallel for rising cold agglutinin antibodies and for specific *Mycoplasma pneumoniae* antibodies as well as to confirm the diagnosis of this infection.

At present, immunofluorescent identification of virus antigen in exfoliated cells is a specialized procedure of limited availability and applicability. Influenza, parainfluenza and respiratory syncytial virus infections of the respiratory tract can be detected by this method. Cells scraped from the nasal or oropharyngeal mucosa are smeared on slides, gently fixed with acetone and overlaid with fluorescein-conjugated antibody to the virus in question; a separate test slide for each serum is required. Although the test can be completed in hours, it requires a skilled technician, careful attention to controls and the availability of certified reagents.

Isolation of the infecting microorganism from respiratory tract secretions can be done quite easily but, unlike bacterial isolation procedures, it requires up to several weeks to recover and identify either viruses or *Mycoplasma pneumoniae*. Nasal swabs, oropharyngeal swabs or sputum specimens are used. For virus isolation, these materials are inoculated into several tubes of tissue cultures, which then are incubated and examined at intervals for evidence of virus growth. By char-

acteristic changes in the cells, a presumptive identification of the isolated virus can be made. Specific identification requires further serologic tests, which may take several weeks to complete. Very often the presumptive identification provides enough information to aid in management of the patient's disease.

For isolation of *Mycoplasma pneumoniae* or other mycoplasmas, the sputum is inoculated onto two plates of PPLO* agar by heavy streaking and one plate is incubated aerobically and the other anaerobically. At 3–4-day intervals, the plates are examined under low-power microscopy for mycoplasma colonies. Since most species of mycoplasma found in the respiratory tract have similar colonial morphology, specific identification of the organism must be made by serologic measures. In a preliminary way, the mycoplasma can be tentatively identified as *Mycoplasma pneumoniae* if it grows aerobically and produces beta hemolysis of guinea pig erythrocytes that are overlaid on mature colonies as a 1% suspension of red blood cells in a light agar solution.

More generally available than either of the above tests, antibody assays provide a specific and relatively easy means for identifying the agent in nonbacterial respiratory infections. Usually acute and convalescent serum specimens are tested simultaneously for a number of organisms known to produce respiratory tract infections. The demonstration of a fourfold or greater rise in antibody from the acute phase specimen to the convalescent phase specimen is evidence of recent infection with that specific agent, if the serum specimens are temporally related to the onset of illness and the convalescence of the patient. Multiple antibody rises, which occur in a number of instances, must be interpreted in light of the known antigenic relationships of viruses and the epidemiologic information on virus prevalence in the community at the time.

Antibody tests are available for all viruses, mycoplasmas, rickettsia and chlamydia organisms. For convenience, diagnostic rises can be sought by means of complement fixation procedures, although the more involved neutralization, hemagglutination-inhibition and immunofluorescent procedures are available for some agents. Cold agglutinins should be de-

*Pleuropneumonia-like organisms.

termined when *Mycoplasma pneumoniae* infection is suspected, although only about half of patients, usually the more severely ill, develop this nonspecific antibody during convalescence. A positive test for cold agglutinins in nonbacterial respiratory infections generally excludes other nonbacterial agents.

Virus Vaccines and Viral Chemotherapy

At present, immunoprophylaxis for the nonbacterial respiratory infections is available only for influenza virus infections. The vaccine comprises the most recently prevalent strains (two type A and a single type B strain) and is a formaldehyde-inactivated, egg-grown antigen. Although experimental inactivated and live attenuated virus vaccines have been prepared and studied in volunteers for the parainfluenza viruses, respiratory syncytial virus and *Mycoplasma pneumoniae,* these vaccines are not licensed for general use and remain in the developmental stages. Because of the large numbers of rhinoviruses (more than 100 types) and enteroviruses (more than 60 types) associated with respiratory tract infections, the development of vaccines for a number of them that are involved in the majority of infections does not seem practicable and other means of direct treatment of these infections must be sought.

Influenza virus vaccine is recommended for persons suffering from chronic debilitating diseases (especially congenital and rheumatic heart disease, hypertensive and arteriosclerotic heart disease, chronic respiratory diseases, diabetes mellitus and chronic metabolic disorders), aged individuals and individuals employed in essential community services. At more or less regular intervals, influenza viruses undergo minor and major changes in surface antigens, requiring the use of the most recently recognized and defined antigenic type in the vaccine. The major surface antigens of influenza A virus include the hemagglutinin and neuramidinase activity of the virus. These antigens may change either singly or together in the prevalent influenza A strain. To achieve effective levels of antibody, the vaccine should be given annually. The course of immunization with inactivated bivalent influenza virus vaccine consists of a single injection of 0.5 ml administered sub-

cutaneously. For persons previously vaccinated, a single injection of 0.5 ml subcutaneously is given on an annual basis.

Live attenuated virus vaccines for influenza virus are being developed. They consist of recombinant strains of influenza virus in which the most prevalent strain is used along with an older nonvirulent strain that induces a high level of antibody. By this method, the recombinant strain induces high levels of antibody to the antigens contained in the recently prevalent strain, and can be produced rapidly. However, such vaccines still are experimental and require additional testing before they can be made available for general use.

At present, there are no effective drugs available for use in the treatment of viral respiratory infections. However, one drug, amantadine (adamantanamine hydrochloride) is available for the specific chemical prophylaxis of influenza type A2 infections. Amantadine impairs the penetration of influenza virus into the host cell and must be given in advance of infection to achieve maximal effect. The drug is given orally, absorbed from the gastrointestinal tract and excreted in the urine. Essentially, the drug should be given to high-risk individuals when outbreaks of influenza virus A2 strains are recognized in the community. The dose for adults is 200 mg daily. Higher daily doses infrequently produce central nervous system side-effects, including nervousness, dizziness, inability to concentrate and depression. In high-risk groups, especially when the level of immunity to the current influenza A2 virus strain might be expected to be low, amantadine can be given along with immunization with inactivated influenza virus vaccine, the medication being continued until an antibody response develops. Amantadine is contraindicated in pregnant women.

In varicella pneumonia, especially in an individual with a defect in antibody production, immune serum globulin can modify the severity of the disease. The dose in adults is 20 ml intramuscularly and in children 0.6 ml/1 lb. Zoster immune globulin is more efficient. It is prepared from patients convalescing from herpes zoster infections and contains a high titer of specific antibody. The dose in adults is 10 ml intramuscularly and for children 0.2 ml/1 kg. It can be obtained from the Center for Disease Control, Atlanta, Georgia.

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