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Mycoplasma pneumoniae Respiratory Infection

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IMPORTANT POINTS

1. *Mycoplasma pneumoniae* remains the most common treatable cause of community-acquired atypical pneumonia in children.
2. Common features of *M pneumoniae* pneumonia include bilateral pulmonary involvement, multifocal or diffuse disease, and reticular infiltrates, but the radiologic manifestations are considerably more diverse.
3. Extrarespiratory manifestations potentially can include several body systems (eg, varied exanthemata, meningoencephalitis, arthropathy). These are either shortly preceded by or coexist with an active respiratory infection.
4. Cold agglutinin serology is of limited diagnostic value for children.
5. Erythromycin and tetracycline remain effective antimycoplasmal antibiotics; beta-lactam agents are not of value.

Introduction

One would anticipate that almost 4 decades of research and clinical experience should leave very little room for ongoing investigation of *Mycoplasma pneumoniae*. Nevertheless, respiratory infection caused by this pathogen remains common, and advances in science continue as unique attributes of the bacterium and the associated clinical illness unfold.

Microbiologic and subsequently other investigations possibly have been delayed in part by the nature of the bacterium. Mycoplasmas are the smallest bacteria, and *M pneumoniae* in particular is sufficiently fastidious in vitro that few laboratories have provided culture services. Whereas *Escherichia coli* from a urine sample or *Streptococcus pneumoniae* from a cerebrospinal fluid specimen may be cultivated luxuriously in 18 to 24 hours, the isolation of *M pneumoniae* from sputum may require 7 to 21 days.

These small, cell wall-deficient bacteria are impossible to visualize in respiratory secretions by either Gram stain or other light microscopic methods. In contrast to the rigid structure of other bacteria, mycoplasmas are pleomorphic (Fig. 1). Indeed, the name myco-

plasma refers to the plasticity of bacterial forms that crudely resemble some fungal filaments. Mycoplasmas, however, are not even remotely related to or even minimally resemble mycobacteria (eg, *Mycobacterium tuberculosis*) or mycologic (ie, fungal) pathogens with respect to most other attributes. The lack of cell wall also is significant because this structure is a major target for beta-lactam antimicrobial activity in most other bacteria. As a practical rule, therefore, beta-lactam antibiotics are ineffectual for *M pneumoniae* infections.

Despite the problems that such a bacterium and its attributes pose, scientists have found some benefit for the tiniest of bacterial genomes. The small amount of DNA has facilitated full DNA sequencing of this bacterium well ahead of other more common bacterial pathogens, and knowledge of the complete genetic code certainly will lead to greater insights (analogous to the benefits of fully defining the human genome).

Epidemiology

Humans are the only apparent reservoir for *M pneumoniae*, and although other human and animal mycoplasmas share some physiologic and structural attributes, this bacterium appears to be the only mycoplasma that has the ability to cause widespread respiratory disease

in the general community. *M genitalium* is a distantly related but more fastidious mycoplasma that some have suggested could be a cause of respiratory disease, but its role in community-acquired respiratory disease remains to be defined. Ureaplasmas, a unique mycoplasmal group commonly found in the human genital tract, have been associated with respiratory disease in the very premature low-birthweight infant, but they do not appear to contribute to other respiratory illnesses.

M pneumoniae is spread from person-to-person presumably by direct contact or by large particle aerosol among close contacts. Epidemics among closed populations have been cited, and it is not uncommon for family members or schoolmates to become infected at weekly intervals. The incubation period is usually 1 to 2 weeks. Infections are seen throughout the year, but school attendance is likely to enhance the spread of infection. Based on the epidemiology of *M pneumoniae* respiratory infection studied since the early 1960s, it was suggested that community epidemics occurred in 4- to 5-year cycles. However, such periodicity has not been as apparent over the past decade, and it has been proposed that increasing use of child care in western countries may have modified the patterns of spread.

M pneumoniae disease seems to be quite uncommon in the first year of life. It is unclear whether this is due to immunity acquired from the mother or to the lack of maturation of respiratory receptors for the bacterium. Infection is more common in school-age children, adolescents, and young adults. Whereas some have viewed *M pneumoniae* primarily as a pathogen of adolescents and young adults, it is clearly very important in the younger pediatric age group, especially after entrance into schools or child care. It is presumed that communicability is enhanced by the increased number of susceptible contacts in a relatively closed setting.

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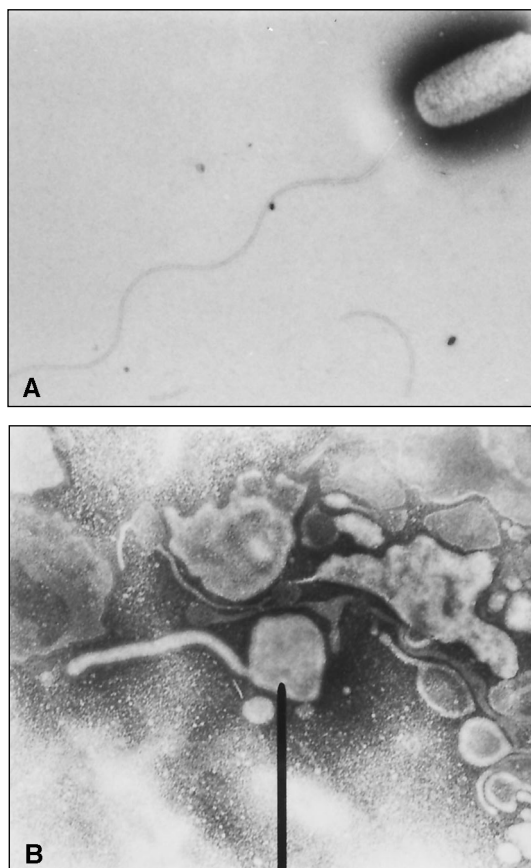


FIGURE 1. A. Typical structure of a common Gram-negative bacterium (*Pseudomonas aeruginosa*) and its flagellum, as seen on electron microscopy. B. Pleomorphic structure of *M pneumoniae*, as seen on electron microscopy. Bacterium is indicated by the black pointer.

Although infection is not any more common in those who are immunocompromised, even these patients will encounter common respiratory pathogens in the community. Severe infection in any patient may reflect an advanced unrecognized illness but also may be due to the existence of copathogens. In some circumstances, it is inevitable that two pathogens co-infect the same individual when both microbes are common community-acquired agents. In other circumstances, pre-existing *M pneumoniae* infection may result in a temporarily modified respiratory tract, leaving that area more susceptible to the next common respiratory pathogen or vice versa.

Pathogenesis

Like many other respiratory pathogens, *M pneumoniae* possesses

specialized attachment proteins that facilitate initial binding to ciliated respiratory epithelial cells. The attachment site, or receptor, is a complex carbohydrate that structurally resembles the I antigen of red blood cells. It is believed that the antibody response to this attachment protein-receptor complex leads to the anti-I antibody, which is the cold agglutinin. Therefore, the cold agglutinin is an autoantibody, not a bacterium-directed response.

Despite understanding the foregoing, it is still unclear what mechanism the bacterium actively employs to harm respiratory mucosal cells. The histopathology of infection is limited primarily to ciliated respiratory epithelium extending from the trachea to the respiratory bronchioles (Fig 2). The airways are surrounded by mononuclear cell infiltrates.

The intraluminal site may contain a combination of polymorphonuclear and mononuclear cells. This pattern is similar to the histopathology of various viral lower respiratory tract infections and may explain why both viruses and *M pneumoniae* can cause clinically indistinguishable community-acquired atypical pneumonia.

Systemic spread of the bacterium is believed to be rare, although this has been reported. The vast majority of *M pneumoniae*-associated illnesses are confined to the respiratory tract, but a wide range of extrapulmonary manifestations are possible (Table 1). On an ambulatory basis, the more common manifestations include red macular rashes and transient arthropathies. More severe extrapulmonary manifestations may include meningoencephalitis and other central nervous system disorders, severe hemolytic

anemia, and carditis. It is critical to recognize that extrapulmonary manifestations are preceded by or coexist with an active respiratory tract infection. It is unclear why such manifestations occur, but some believe that an autoantibody may be partially responsible. This enigma continues.

Clinical Aspects

SYMPTOMS

The presenting clinical symptoms of *M pneumoniae* infection are non-specific and as with many viral respiratory infections, the illness often progresses from the upper to the lower respiratory tract. Initially, patients may manifest symptoms of mild pharyngitis, although rhinorrhea and presentation as a "head cold" are uncommon. Within a few days, the infection progresses to involve the large airways. This tracheobronchitis may be the end stage of infection, although this can progress to pneumonia in a lesser proportion of patients. Fever and sputum production are common, but they are not as severe as seen in more typical bacterial pneumonias such as pneumococcal pneumonia. Otitis media and sinusitis are uncommon accompaniments. In convalescence, a postinfectious bronchitis may continue for weeks. Typically, the progression from early stages of symptomatic infection to pneumonia requires 6 to 10 days.

In some circumstances, *M pneumoniae* infection may complicate the asthmatic respiratory tract. In this context, the potential for progression to the more severe spectrum of respiratory infection is increased. Indeed, an acute asthmatic attack may be the primary manifestation that leads to medical care. When extrapulmonary manifestations occur, they almost always are preceded by some type of respiratory illness.

SIGNS

A few signs can increase the suspicion of *M pneumoniae* in a respiratory tract infection. Bilateral and scattered pulmonary involvement may be consistent with this infection but are not specific for it. Further-

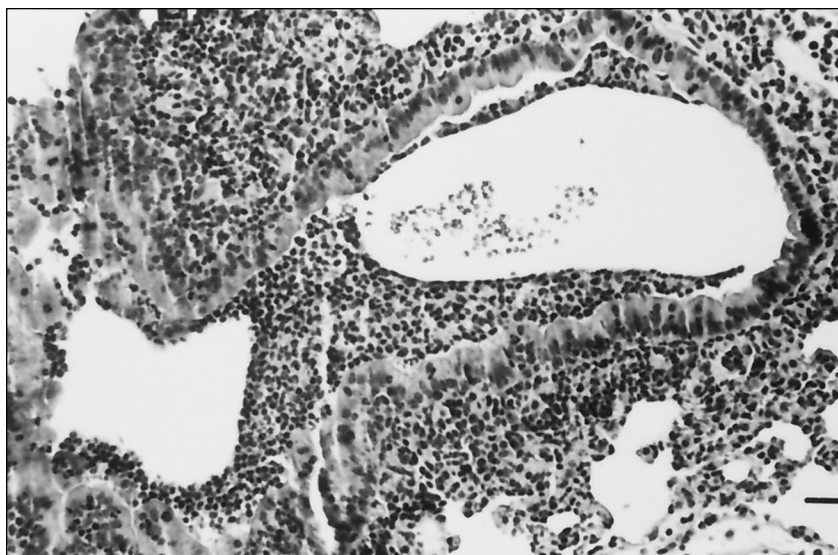


FIGURE 2. Histopathologic study of *M pneumoniae*-infected lung tissue. The respiratory bronchiole is surrounded by an inflammatory mononuclear cell response. The intraluminal site is approximately 30% occluded by mucus and white blood cells.

more, some patients may have unifocal, segmental disease. Major consolidation is uncommon. Bilateral bullous myringitis is said by some to be highly suggestive, but this sign is relatively rare. The pattern of lower respiratory tract infection associated with extrapulmonary sign(s) also may be suggestive (eg, lower respiratory tract infection associated with Stevens-Johnson syndrome), but again this is not common (<10%).

Among older children and adolescents who may be able to produce a sputum specimen for evaluation, the Gram stain will show an inflammatory response but no dominant bacterial morphotype. Therefore, a sputum specimen that exhibits polymorphonuclear cells (especially mononuclear cells) but no obvious bacterial forms should raise the suspicion for *M pneumoniae*. The white blood cell count usually is within the normal range; in advanced disease, elevations are seen occasionally. In these cases, a link with a secondary bacterial agent (ie, superinfection) should be considered.

RADIOLOGIC FEATURES

It has been convenient to regard *M pneumoniae* as a cause of community-acquired atypical pneumonia, with the entity depending in large part on radiologic features. Prominent among these features are bilateral pulmonary involvement, multifocal or diffuse disease, and reticular

infiltrates. Nevertheless, the radiologic appearances can be quite diverse, and they may mimic other bacterial lobar pneumonias. Examples of the latter may include right middle lobe or unilateral apical disease (Fig. 3). Pleural effusions may be superimposed on parenchymal disease, and in late convalescence, effusions may be the only pathology remaining to compromise respiratory function. Discordance between the magnitude of radiologic change and the severity of clinical illness is not uncommon.

Differential Diagnosis

It is evident that many infectious agents are capable of causing similar clinical respiratory manifestations to *M pneumoniae* disease. In immunocompetent children and teenagers, most of these agents will be respiratory viruses, especially adenovirus, parainfluenza viruses, and influenza viruses. Mild forms of predominantly upper and middle respiratory tract infection may be mimicked by a wide array of viruses, including rhinoviruses, coronaviruses, and respiratory syncytial virus. *Chlamydia pneumoniae* also has been recognized as a pediatric pathogen of atypical pneumonia, but there is considerable controversy about its frequency. Most studies indicate infrequency of the latter infection in the preschool years and an

TABLE 1. Extrapulmonary Manifestations of *Mycoplasma pneumoniae* Infection

<ul style="list-style-type: none"> • Dermatologic (exanthemata) <ul style="list-style-type: none"> – Erythema (macular) – Stevens-Johnson syndrome – Urticaria – Vesicles
<ul style="list-style-type: none"> • Neurologic <ul style="list-style-type: none"> – Cranial neuropathy – Meningoencephalitis – Transverse myelitis – Cerebral infarction – Guillain-Barré syndrome
<ul style="list-style-type: none"> • Arthropathic <ul style="list-style-type: none"> – Acute arthritis
<ul style="list-style-type: none"> • Hematologic <ul style="list-style-type: none"> – Immune hemolytic anemia
<ul style="list-style-type: none"> • Cardiac <ul style="list-style-type: none"> – Pericarditis – Myocarditis

incrementally greater but still relatively low frequency in older children. Other atypical pneumonia agents include *Legionella*, Q fever (*Coxiella*), and spotted fever rickettsiae. In addition, a great number of noninfectious illnesses may result in atypical pneumonia-like radiologic patterns of pulmonary infiltrates. Careful consideration of clinical variables is critical to assigning higher probability to any of these concerns.

For patients who are immunocompromised, the differential diagnosis must be expanded to include opportunistic agents, but the condition of immunocompromise should not discourage concern for typical community-acquired agents such as *M pneumoniae*.

Laboratory Diagnosis

As previously detailed, bacterial culture is of little practical value for most patients. Consequently, serologic diagnosis has been the mainstay of laboratory testing. Cold agglutinins were linked to atypical pneumonia well before the etiologic agent was discovered more than 3 decades ago. Cold agglutinins are immunoglobulin M (IgM) anti-I red blood cell antigen antibodies that agglutinate I-contain-

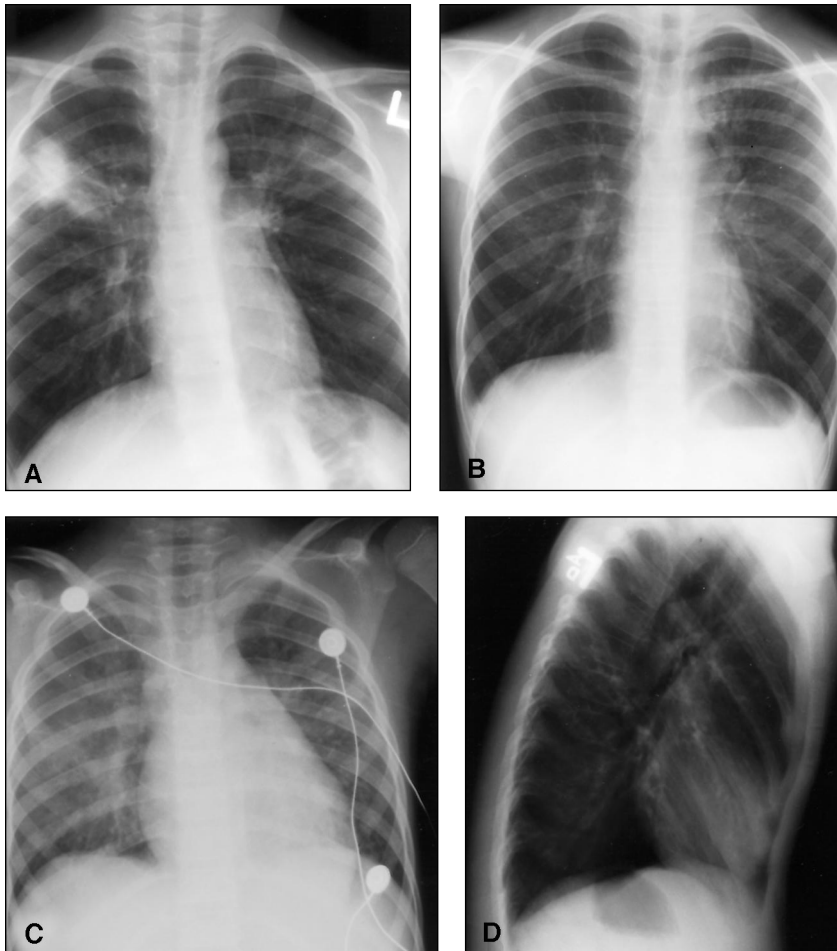


FIGURE 3. Radiologic features of *M pneumoniae pneumonia*. A. Bilateral pneumonia with major foci in the right upper, right middle, and left upper lobes. B. Bilateral reticular pattern with accentuated left upper lobe involvement. C. Bilateral diffuse pneumonia with accentuation in the right lobes. D. Lateral view of the chest illustrating concentration of disease in the right middle lobe.

ing red blood cells. These antibodies are not directed specifically at bacterial antigens (ie, they are a type of heterophil antibody), but they may serve as a diagnostic marker.

In adolescents and adults, a high titer (eg, $\geq 1/64$) of cold agglutinins is reliably diagnostic of *M pneumoniae* infection when the patient clearly has a lower respiratory tract illness. Unfortunately, only about 50% of adolescents who have atypical pneumonia will exhibit such high titers of cold agglutinins. Lowering the threshold for what is considered a significant titer will lead to considerable nonspecificity. For children younger than age 12 years, cold agglutinin serology is both insensitive and nonspecific. For example, a wide range of viral respiratory infections occasionally can be associated with low titers of

cold agglutinins. Because the laboratory work required to assess cold agglutinin status is not inconsequential, many have recommended against requesting cold agglutinins for pediatric age groups.

Complement fixation (CF) serology has been validated and used for decades and continues to be available. Acute and appropriately timed convalescent serum pairs will capture the majority of diagnoses, but acute sera alone for the CF test will miss approximately 40% to 70% of the diagnoses. The complexity of the CF test has mandated that it be performed in large laboratories, often reference state/provincial laboratories, a requisite that has contributed to delay in obtaining timely results. Accordingly, there has been great interest in creating assays that detect IgM antibody, bacterial antigen, or

genetic material specific to *M pneumoniae*.

Direct antigen detection has not yet proven of value. Several anti-*M pneumoniae* IgM detection tests (IgM as a marker of acute infection) have enjoyed widespread use, but they must be used appropriately within the context of the infection. IgM serology depends on sufficient time for the humoral immune response to have been generated; 6 to 10 days of total clinical illness often are required before IgM can be detected.

Direct tests for bacterial genome are emerging. Early DNA probes proved to be sufficiently insensitive for routine use. The newest generation of direct detection assays use the polymerase chain reaction (PCR) technology, which is capable of detecting small quantities of bacterial genome through biochemical amplification of DNA from clinical specimens. The potential benefit of this technique is that it is not necessary to wait for an immune response, making earlier detection possible. The availability of this technology will expand, but pediatricians should consult their laboratory services to determine availability at this time.

When a laboratory diagnostic test for *M pneumoniae* infection is required, the clinical circumstances will determine the diagnostic route. For example, a timely IgM assay may be sufficient for immunocompetent children who have atypical pneumonia and have been ill for 8 to 10 days. In contrast, direct genetic detection by a PCR assay, if available, is more likely to be of value in an immunocompromised child who has been ill for 5 days. Diagnostic paradigms are certain to follow as these new assays become more available.

In an era of health-care cost constraint, it is important to consider the costs and benefits of any diagnostic test. It has been our experience that an efficient rapid diagnostic test may be used more in the short-term, but may be used sparingly after physicians become better acquainted with a disease that was less well understood because of the lack of accurate diagnostic tools.

Treatment

The value of either erythromycin or tetracycline for the treatment of *M pneumoniae* pneumonia is well documented (Table 2). It has been inferred that such antibiotics should be of value for the treatment of moderate-to-severe *M pneumoniae*-associated tracheobronchitis when an antibiotic intervention may be desirable. It also has been extrapolated by some practitioners that antibiotics may be of value in late postinfectious bronchitis (eg, 3 to 5 wk after initial disease). The latter use has not been clearly justified, and it has probably been overused either because of the concern for suprainfection by another bacterial pathogen or because there may be little to offer these patients apart from expectant resolution.

Erythromycin continues to be the drug of choice in most pediatric circumstances. Such use is favored because this agent is effective against several of the other bacterial agents of atypical pneumonia and against many more typical bacterial pneumonia agents, such as pneumococci and staphylococci. Some have suggested that erythromycin alone could be a single empiric agent for community-acquired lower respiratory tract infections in previously well children. It cannot be underestimated, however, that individual contexts may prompt reconsideration of any empiric antibiotic regimen. Despite pharmacologic variability, the specific form of erythromycin (eg, base versus estolate versus ethylsuccinate versus stearate) employed does not appear to matter. If a rash is associated with an erythromycin conjugate, use of the base has been acceptable. Nevertheless, complaints of abdominal discomfort and nausea with pediatric use continue.

It is not surprising that many physicians choose macrolide alternatives such as clarithromycin and azithromycin because of lesser intolerance associated with these agents. These antibiotics appear to have equivalent antibacterial activity, and the consensus of available data supports their use, although they

Preferred	
Erythromycin base	30 to 50 mg/kg per day
Erythromycin estolate	(divided into 4 doses;
Erythromycin ethylsuccinate	maximum, 500 mg qid)
Erythromycin stearate	
Tetracycline (for children ≥10 years of age)	25 to 50 mg/kg per day (divided into 4 doses; maximum, 500 mg qid)
Alternative	
Clarithromycin	15 mg/kg per day (divided into 2 doses; maximum, 500 mg/dose)
Azithromycin	10 to 12 mg/kg per day (single dose; maximum, 500 mg/dose)
Doxycycline (for children ≥10 years of age)	2 to 4 mg/kg per day (divided into 2 doses; maximum, 100 mg bid)
Not Effective	
Beta-lactam agents	
Trimethoprim-sulfamethoxazole	

are considerably more expensive than erythromycin.

Tetracycline should be considered for the child 10 years and older. The antibiotic is effective, inexpensive, and generally well tolerated. Doxycycline is a more expensive albeit equally effective alternative.

Beta-lactam agents generally should not be used. Regardless of advances in cephalosporin development, these agents do not play a role in the treatment of primary mycoplasmal infection. Concern for a bacterial suprainfection, however, or uncertainty over the role of *M pneumoniae* as the primary cause has led some to use both erythromycin and a second-generation cephalosporin for initial therapy of severe acute community-acquired pneumonia in children who are admitted to hospital.

Length of therapy is more controversial, but pneumonia should be treated for approximately 7 to 10 days because clinical relapse has occurred in some patients who have had shorter courses of therapy. The conversion of intravenous to oral

therapy or the use of oral therapy only for the duration of the illness is still the subject of individual discretion, but several investigators are examining short-term use of new macrolides.

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PIR QUIZ

1. Infection with *Mycoplasma pneumoniae* is best characterized by:
 - A. A reservoir in domestic pets.
 - B. Infrequent disease among infants younger than 18 months.
 - C. Predominance in spring and summer.
 - D. Transmission by an arthropod vector.
 - E. Uncommon intrafamilial spread.
2. The extrapulmonary manifestation most likely to occur in a previously healthy 10-year-old boy who has *Mycoplasma pneumoniae* pneumonia is:
 - A. Aplastic anemia.
 - B. Chronic arthritis.
 - C. Macular exanthem.
 - D. Myocarditis.
 - E. Transverse myelitis.
3. *Mycoplasma pneumoniae* pneumonia is least likely if chest radiography reveals:
 - A. Bilateral disease.
 - B. Cavitation.
 - C. Lobar consolidation.
 - D. Multifocal disease.
 - E. Pleural effusion.
4. A 10-year-old girl has had a slightly productive cough for the past 2 weeks. She is afebrile and not toxic. Auscultation detects a few crackles in the left lower lobe. Chest radiography reveals a reticular infiltrate. You suspect *Mycoplasma pneumoniae* infection. The best current choice of diagnostic test is:
 - A. Acute serum complement fixation.
 - B. Bacterial culture.
 - C. *Mycoplasma*-specific immunoglobulin M (IgM).
 - D. Serum cold agglutinins.
 - E. Sputum Gram stain.
5. You confirm that pneumonia in a previously well, nontoxic, 12-year-old boy is caused by *Mycoplasma pneumoniae*. The most cost-effective choice of therapy is:
 - A. Amoxicillin.
 - B. Azithromycin.
 - C. Ciprofloxacin.
 - D. Clarithromycin.
 - E. Tetracycline.

ERRATUM

Previous articles* in *Pediatrics in Review* have stated that rabies is a uniformly fatal disease, which, of course, is what most of us were taught. However, Dr Thomas Weis points out that the 1997 *Red Book* states, "only seven patients with human rabies have survived with intensive, supportive care...." As Dr Weis states, "Though the odds are small, each rabies victim should be given the chance of living."

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