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Mycoplasma pneumoniae Pneumonia

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Mycoplasma pneumoniae is a common cause of community-acquired pneumonia (CAP). Results of recent studies indicate this pathogen may cause 5% to 30% (in selected populations) of cases of CAP (Table 1). Although most often described as a respiratory pathogen associated with mild disease and primarily in young patients, *M. pneumoniae* may cause pneumonia in all age groups and can be fatal; in some persons the organism has the ability to produce invasive infection resulting in serious complications (Cassell, 1995).

Microbiology and Pathogenesis

M. pneumoniae is a cell wall-deficient bacterium with a sterol-containing plasma membrane (Baseman & Tully, 1997). Mycoplasmas will grow on cell-free media but they require a sterol-containing medium supplemented with horse serum and fresh yeast extract for growth (Liu, 1994). *M. pneumoniae* is facultatively microaerophilic and differs from other mycoplasmas in that it ferments glucose and hemolyses erythrocytes. Isolation from clinical specimens is relatively slow, requiring 2 to 3 weeks for visible growth.

Mycoplasma infects the respiratory tract extracellularly as filamentous forms that adhere to epithelial cells (Baseman & Tully, 1997; Baum, 1995). Cell injury which occurs after attachment can lead to ciliostasis, which may account for the prolonged paroxysmal cough that often occurs. Pathological findings in fatal cases of *M. pneumoniae* pneumonia include diffuse pneumonia associated with alveolar infiltrates, hyaline membrane formation, and pulmonary infarcts. Other pathological findings have been adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and interstitial fibrosis (Baum, 1995). Open-lung biopsies in six patients with nonfatal *M. pneumoniae* pneumonia reported in a recent review revealed infiltration of bronchiolar walls with acute and chronic inflammatory cells (cellular bronchiolitis) in two patients, bronchiolitis obliterans with organizing pneumonia in three patients, and an active pneumonitis in one patient (Chan & Welsh, 1995).

The exact pathogenesis of *M. pneumoniae* infection in humans is unclear. Two mechanisms for development of disease may play a major role: tissue reaction directly as a result of microbial invasion or an autoimmune-mediated process.

In experimental animal models of intranasally inoculated *Mycoplasma* infection the organism quickly attaches to the epithelial cells of the upper respiratory tract, which appears to serve as a nidus of infection from which the organism can be transmitted to other animals or spread to the lower respiratory tract (Cassell, 1982). *Mycoplasma* can be readily isolated from the lung tissue of these infected animals (Cartner et al., 1995). Lung findings included neutrophil-rich exudate in airways; hyperplasia and dysplasia of the airway epithelium; submucosal lymphoid hyperplasia; peribronchiolar, bronchial, and perivascular infiltrates; luminal occlusion; and parenchyorial pneumonia (Cartner et al., 1995; Wubbel et al., 1998). Evidence indicates that mycoplasmas cause direct cell injury following

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TABLE 1. Percent of Community-Acquired Pneumonia Cases Caused by *Mycoplasma pneumoniae*

Study	No. of patients	Type of patients	Method of diagnosis	% due to *M. pneumoniae*
Marrie et al., 1989	301	Hospitalized adults	Serology	5.6
Fang et al., 1990	359	Hospitalized adults	Serology	2 (1)
Mundy et al., 1995	385[a]	Hospitalized adults	PCR	0.8 (0.8)[b]
Lieberman et al., 1996a	348	Hospitalized adults (HIV excluded)	Serology	29.2
Gray et al., 1997	88	Hospitalized adults; military recruits	Serology, culture, PCR	36.4
Marston et al., 1997	2775	Hospitalized adults	Serology	31 (5.3)
Cassell et al., 1991	120	Adult outpatients	Serology, culture	13
Block et al., 1995	260	Pediatric outpatients	Cultures, serology, PCR	27
Marrie et al., 1996	149	Adult outpatients	Serology	26

PCR, polymerase chain reaction.
[a]45% with HIV infection.
[b]Parentheses indicate percentage with definite diagnostic criteria, see text.

attachment. Ciliostasis, loss of cilia, distention of intracellular spaces, cytoplasmic vacuolization, disruption of mitochondria, and epithelial hyperplasia and metaplasia have been observed in animal models (Cassell, 1982).

Immune mechanisms may also be important in the pathogenesis of *M. pneumoniae* pneumonia. One of the properties of *Mycoplasma* attachment-related proteins is their extensive homology to mammalian structural proteins. An immune response to these cytoadherence proteins may trigger an autoimmune response (Baseman & Tully, 1997). Patients with documented *M. pneumoniae* respiratory infection demonstrate seroconversion to myosin, keratin, and other tissue proteins, and often manifest extrapulmonary findings such as immune hemolytic anemia, exanthems, and cardiac and central nervous system abnormalities. The multi-organ protean manifestations of *Mycoplasma* infection are consistent with the pathogenesis of autoimmunity (Murray et al., 1975; Baseman & Tully, 1997). The relative importance of direct *Mycoplasma* damage as opposed to immune inflammatory reactions in infection has not been determined.

Prevalence and Epidemiology

In clinical practice, *M. pneumoniae* is often suspected but confirmatory tests are seldom performed. Cases of these infections, therefore, tend to be underdiagnosed. The relative prevalence of CAP attributed to *M. pneumoniae* is derived from the results of numerous studies that have evaluated the etiologic agents of CAP using various bacteriologic and immunologic tests. As indicated in Table 1, the percentage of cases of CAP caused by *M. pneumoniae* ranged from 0.8% of cases requiring hospitalization at a tertiary medical center (Mundy et al., 1995) to 36% of cases among U.S. military personnel in training (Gray et al., 1997). The relative rates for these studies will vary depending on the criteria for diagnosis (loosely or strictly applied), age group, geographic location, and whether an epidemic is occurring at the time of evaluation. Only a few studies classify etiologic diagnosis as definite, probable, or possible based on specification of the diagnostic method. Diagnosis based on a single-titer IgG antibody result is less definitive than a 4-fold rise and may falsely include a case. Therefore, an attempt to compare various studies can be problematic. Two recent series illustrate these differences. Mundy et al. (1995) prospectively evaluated 385 patients hospitalized at Johns Hopkins Hospital (45% were infected with HIV). At 0.8%, the incidence of *M. pneumoniae* was very low. However, the diagnosis was based solely on positive culture or polymerase chain reaction. Leiberman et al. (1996a) evaluated 346 CAP patients in a hospital in southern Israel and reported that *M. pneumoniae* was identified in 29.2% of the patients—in many patients more than one pathogen was identified. A large proportion of cases were diagnosed by serologic means (with a single elevated titer as a

criterion). In this study *M. pneumoniae* was the most common cause of CAP in patients 17 to 44 years of age, accounting for 43.2% of cases in this age group. In a recent prospective study of 2776 adult patients hospitalized with CAP from Ohio, *M. pneumoniae* accounted for 5.3% (using criteria for definite diagnosis) to 31% (including criteria for possible diagnosis) of patients (Marston et al., 1997).

In general, *M. pneumoniae* is a common cause of CAP in ambulatory patients and is implicated in 13% to 27% of cases of CAP in the studies reviewed. Although some studies have found *M. pneumoniae* to be an uncommon case of CAP in adults requiring hospitalization (Janssens et al., 1996), the Ohio study observed this to be an important cause of CAP in both persons younger than 50 years as well as in older age groups (Marston et al., 1997). This study found that the incidence of *M. pneumoniae* in older adults increased with age (Fig. 1), with an incidence in the 65–84 year age group of 25 per 1000 and in the ≥85 year age group of 45 per 1000 (Marston et al., 1997). Others have also reported *M. pneumoniae* as a significant cause of pneumonia in older adults and pneumonia requiring hospitalization (Lim et al., 1989; Lieberman et al., 1996b).

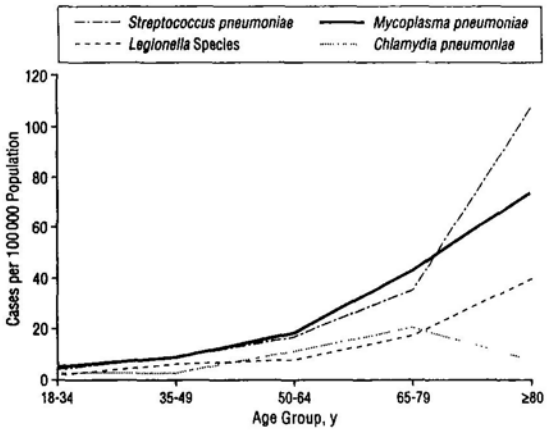

FIGURE 1. Age-specific rates of hospital admission for community-acquired pneumonia due to *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella*. Reproduced, with permission, from Marston et al., 1997.

M. pneumoniae infections are ubiquitous and must be considered as a potential cause of CAP in virtually all age groups in both urban and rural settings. Early longitudinal studies found that the rate of infection of *M. pneumoniae* was highest among school children and second highest among children <5 years of age (Foy et al., 1970). Recent studies have also found *M. pneumoniae* to be a common cause of pneumonia in children aged 3 through 12 (Block et al., 1995). Including patients treated within or outside the hospital, Foy et al. (1979) reported the incidence of *M. pneumoniae* pneumonia as 500/100,000 per year for the age 10 population, with a steady reduction in incidence to less than 100/100,000 per year for the population older than age 70 (Foy et al., 1979).

Although objective confirmation is often difficult, *M. pneumoniae* can be associated with pneumonia caused by mixed infection. The incidence of CAP caused by more than one apparent etiology that includes *M. pneumoniae* varies among different studies and, to a certain extent, depends on the definition (i.e., definite vs. presumed) of the diagnosis. The mixed infections observed in studies are often caused by *M. pneumoniae* and a bacterial agent such as *S. pneumoniae.* In such cases, *M. pneumoniae* may be the initiating pathogen and, after immobilizing the ciliated cells lining the respiratory tract, permit a secondary invader, such as *Streptococcus pneumoniae,* to gain access to the lungs. Cimolai et al. (1995) reviewed studies of dual infections that possibly involved *M. pneumoniae.* Co-pathogens predominantly included typical respiratory viruses but also *Haemophilus influenzae,* Epstein-Barr virus, *Coxiella burnetii,* and *Leptospira* spp. (Cimolai et al., 1995). Two recently published trials found very different results concerning the incidence of mixed infections including *M. pneumoniae.* Lieberman et al. (1996a) found mixed infections with *M. pneumoniae* and other pathogens in 48 of 385 (13%) patients with CAP requiring hospitalization. The most common associated pathogen was *S. pneumoniae* in 43 cases. Using a stricter criteria for the definition of etiology, Mundy et al. (1995) found only I of 380 (0.3%) patients with pneumonia due to *M. pneumoniae* and another apparent cause *(Legionella).* It is unclear from such studies whether these mixed infections represent true co-infection, possible sequential infection, or

false-positive findings from serologic tests (particularly when only a single elevated titer is used as the criterion). It is also unclear whether such mixed infections are associated with a worse outcome; Cimolai et al. (1995) describe cases of severe CAP caused by *M. pneumoniae* with other co-pathogens, suggesting more severe disease when more than one pathogen is implicated.

In urban areas, infection tends to be endemic and usually occurs throughout the year; epidemics often occur in cyclical 4- to 7-year intervals. Person-to-person transmission occurs via respiratory droplets. Spread is slow and occurs more often in closed populations such as families or the military. The incubation period is approximately 2 to 3 weeks. Risk factors such as smoking or the presence of comorbid conditions (which are associated with most causes of CAP) are not as significant for *M. pneumoniae.* Several reports have emphasized an unusually increased severity of *M. pneumoniae* infection in patients with sickle cell disease or related hemoglobinopathies, and in children with Down syndrome (Shulman et al., 1972; Solanki & Berdoff, 1979; Orlieck et al., 1992).

Perspectives on the Classification of Atypical Pathogens

M. pneumoniae has been classified with other organisms (e.g., *Chlamydia pneumoniae* and *Legionella* species, and occasionally *Coxiella burnetii)* as pathogens causing atypical pneumonia and has been designated an atypical pathogen (distinct from typical pneumonia pathogens such as *S. pneumoniae).* This designation is controversial in relationship to scientific merit, and it has been suggested by many authorities that the term *atypical* be discontinued (Fang et al., 1990). However, the term remains popular among clinicians of all disciplines.

The term *atypical pneumonia* was first coined by Rieman (1938) when he described several cases of pneumonia caused by an unknown agent and characterized by constitutional symptoms, upper and lower respiratory tract symptoms and signs, and a protracted course with gradual resolution. These cases differed from pneumococcal pneumonia by the lack of typical findings of consolidation and lack of response to penicillin therapy. Since no causative agent could be identified at that time the word *primary* was eventually added, creating the term known for many years as *primary typical pneumonia* (PAP). In the 1940s Eaton et al. (1944) ultimately identified an agent that was the principal cause of PAP, which was eventually identified as *M. pneumoniae.* Subsequently other pathogens have been linked with atypical pneumonia because of similar clinical presentation, including a variety of respiratory viruses, *Chlamydia psittaci, C. burnetii,* and most recently, *C. pneumoniae.* In addition, pneumonia caused by *Legionella* species, although often significantly different in clinical presentation, is also included.

Originally the classification of pneumonia into atypical and typical forms arose from the observation that the clinical presentation of patients were different compared with standard pneumococcal infection. The potential to differentiate the etiology on the basis of presenting manifestations has clinical relevance since rapid diagnostic tests are not readily available for many of these respiratory pathogens and antimicrobial therapy differs from that for standard bacterial pneumonia. The designation of specific clinical features to an etiologic agent has been common practice. Nonetheless, recent data have cast doubt on the specificity of these observations when comparing individual clinical manifestations, concluding that there is excessive overlap of clinical manifestations of specific infectious and noninfectious causes of lung infiltrates, thus, therapeutic decisions cannot be made on the basis of this information (Fang et al., 1990; Farr et al., 1989; Lieberman et al., 1996b). The optimal method of differentiating the increasing number of possible pathogens will be the development of rapid, easily accessible, and cost-effective diagnostic tests.

Clinical Characteristics

M. pneumoniae is a common cause of respiratory infections ranging from asymptomatic infection to upper respiratory tract infection, tracheobronchitis, and pneumonia (Foy, 1993). It is estimated that only 3% to 10% of infected persons develop pneumonia (Clyde, 1993). The majority of patients with symptomatic *M. pneumoniae* infection probably develop

upper respiratory tract infection or tracheobronchitis syndrome.

Pulmonary Manifestations

M. pneumoniae pneumonia is considered to be the classic atypical pneumonia. Early descriptions of the clinical course were based on definite diagnostic criteria (i.e., culture or 4-fold antibody titer rise) and therefore likely represent valid association of findings (Alexander et al., 1986; Foy et al., 1970). The onset is often insidious, over several days to a week. Constitutional symptoms include headache (usually worse with cough), malaise, myalgias, and sore throat. Cough is typically dry, paroxysmal, and worse at night and may produce mucopurulent sputum. Sinus and ear pain are occasionally reported. The physical findings often are minimal, seemingly disproportional to the patient's complaints. Auscultation of the lungs usually reveals variable scattered rales or wheezes. An association between respiratory infection with *M. pneumoniae* and exacerbation of asthma has been established (Laitinen et al., 1992). Abnormalities of ventilatory function as measured by spirometry is likely to be prolonged for several months in patients with *M. pneumoniae* pneumonia (Laitinen et al., 1992). Bullous myringitis, first described in volunteer subjects infected with *M. pneumoniae,* is infrequent in naturally occurring infection. Table 2 lists the clinical manifestations, as reported in reviews and individual studies, of patients with *M. pneumoniae* pneumonia.

Chest radiographic findings are variable and can mimic a wide variety of other conditions. Radiographic findings are related to the pathologic changes, including peribronchial interstitial infiltrates as well as alveolar space neutrophilic infiltration. Common findings include peribronchial pneumonia and localized lower-lobe patchy and consolidating infiltrates. Other patterns include atelectasis, nodular infiltrates, and hilar adenopathy. Clyde (1993) described the most common radiographic findings as peribronchial pneumonia characterized by thickened bronchial shadows, interstitial streaking, and small areas of subsegmental atelectasis. In a series of 76 patients (aged 9 months to 72 years) hospitalized for *M. pneumoniae* pneumonia, Hwang et al. (1993) described peribronchial and perivascular interstitial infiltrates in 18.4%, nonhomogeneous patch consolidation in 22.4%, homogeneous acinar consolidation in 27.6%, and mixed interstitial and alveolar infiltrates in 31.6% of patients. Twenty percent were bilateral and 33% were described as multilobar (Hwang et al., 1993). In a series of 101 adult patients admitted for *M. pneumoniae* pneumonia, a homogeneous infiltrate was found in 45.5%, a patchy infiltrate in 52.5%, and an interstitial infiltrate in 2.0% of patients. The infiltrate was in the right lung in 51.5%, in the left lung in 38.6, and bilateral in 10% of patients; 13% had involvement of more than one lobe (Lieberman et al., 1996b). Although pleural effusion was previously thought to be uncommon in *M. pneumoniae* pneumonia, small effusions can be demonstrated in 2% to 10% of patients with the use of lateral decubitus chest radiographs (Cassell, 1995).

The mortality associated with *M. pneumoniae* pneumonia is low. In a meta-analysis of studies of CAP by Fine et al. (1996), the mortality rate from *M. pneumoniae* infection was 1.4% (compared to 10% for all cases of CAP). Although the clinical course of *M. pneumoniae* pneumonia is usually mild, significant pulmonary complications can occur and include lung abscess, pneumothorax, pneumatocele, bronchiectasis, interstitial fibrosis, and respiratory distress syndrome (Baum, 1995; Chan & Welsh, 1995; Chiou et al., 1997). *M. pneumoniae* has also been reported as a cause of bronchiolitis obliterans organizing pneumonia (Llibre et al., 1997). Chan and Welsh (1995) reviewed 39 cases of *M. pneumoniae* pneumonia that resulted in respiratory failure or death. Most patients were less than 40 years of age, had no underlying disease, and were previously healthy. The reviewers reported a spectrum of small airways disease, including cellular bronchiolitis and bronchiolitis obliterans with and without organizing pneumonia. ARDS and/or DIG was evident in several patients. The incidence of pulmonary thromboembolic disease was increased in fatal cases. The authors suggested that because of the high frequency of acute infection with *M. pneumoniae,* severe cases are probably undiagnosed due to a lack of awareness of such cases. In an additional analysis of *M. pneumoniae* pneumonia requiring hospitalization, with emphasis on infection in the elderly, Marrie (1993) described six patients who were ≥65 years of age.

TABLE 2. Symptoms and Findings in Patients with *Mycoplasma pneumoniae* Pneumonia

	Foy et al., 1970	Mansel et al., 1989	Hwang et al., 1993	Marrie, 1996
No. of patients	385	148	76	
Age group studied	6 months–66 years (15% adults)	3 months–77 years (10% >40 years)	Mean 16–20 years	
Diagnostic methods	Culture: 4-fold antibody rise	Culture: serology	Complement fixation; cold agglutinins	
Symptoms				
Cough	99	97	100	95
Fever	94	—	100	90
Productive cough	45	—	37	83
Anorexia	—	—	—	80
Chills	58	32	33	75
Headache	66	33	30	60
Myalgia	—	24	29 (or arthralgia)	53
Chest pain	NS	25	20	43
Sore throat	54	52	—	33
Arthralgia	—	—	—	30
Nausea	29 (or vomiting)	42	55 (or vomiting)	30
Vomiting	—	—	—	25
Abdominal pain	—	—	—	10
Diarrhea	15	—	—	5
Hoarseness	37	—	NS	NS
Malaise	89	—	NS	NS
Earache	31	—	NS	NS
Rash	15	—	7	NS
Rhinorrhea	29 (coryza)	22	37	NS
Findings				
Temperature	94% >37.8°C	85% >37°C	Mean 37.7°C	92% >37°C (mean = 38.3°C)
WBC >10,000	27% (5% >15,000)	—	—	NS
Crackles	—	—	100	88
Wheezing	—	—	50	20
Consolidation	—	26	33	23
Pharyngeal erythomia	—	47	—	—
CNS involvement	—	7	—	—
Rash	—	6	—	—

NS, not stated or studied; WBC, white blood cell count; CNS, central nervous system.

None of the elderly patients had a discharge diagnosis of *M. pneumoniae* pneumonia. The clinical features of these elderly patients did not allow distinction from other causes of pneumonia. Of the patients that were ≤64 years of age in this series, Marrie (1993) described several underemphasized features of *M. pneumoniae* infection such as prolonged thrombocytopenia, recurrent pulmonary hemorrhage, or thrombostasis. Although not commonly considered, *M. pneumoniae* can be a causative agent of pneumonia in the immunocompromised host (Perez & Heigh, 1991).

In general, while these signs and symptoms are typical of *M. pneumoniae* pneumonia, they are not specific and can be seen with other causes of pneumonia, especially *C. pneumoniae*. However, in one large study of CAP in Seattle, Foy et al. (1970) compared the clinical manifestations of patients

from whom *M. pneumoniae* was isolated to those from whom it was not. Positive correlations with *M. pneumoniae* infection included the presence of headache, rash, sore throat, and a family with more than four members.

Extrapulmonary Manifestations

M. pneumoniae pneumonia is associated with several extrapulmonary manifestations (Table 3) (Murray et al., 1975; Cunha & Ortega, 1996; File et al., 1998; Baum, 1995).

Skin manifestations include maculopapular eruptions, vesicular eruption, toxic epidermolysis, urticaria, erythema nodosum, erythema multiforme, and leukocytoclastic vasculitis (Cherry, 1993; Perez et al., 1997). Mucocutaneous lesions occur in approximately 25% of serologically or culturally documented cases (Cassell, 1995). Erythematous maculopapular or vesicular exanthems are most common. The development of erythema multiforme (including Stevens–Johnson syndrome) associated with CAP is very suggestive of *M. pneumoniae.*

Central nervous system (CNS) complications associated with *M. pneumoniae* infection have been frequently described (Koshiniemi, 1993; Pellegrini et al., 1996; Tjhie et al., 1997). Neurologic manifestations include aseptic meningitis, meningoencephalitis, cerebral ataxia, Guillain-Barré syndrome, and transverse myelitis. The precise incidence has not been determined. Recovery from neurologic dysfunction has often been slow, requiring many months. Up to 10% of cases have been fatal, and about one third who have recovered have permanent neurologic deficit. It has been estimated that 0.1% of all patients with *M. pneumoniae* infection and 7% requiring hospitalization have CNS complications (Cassell, 1995; Koshiniemi, 1993). Although infection has been documented in the CNS by cultural isolation of *M. pneumoniae* from cerebrospinal fluid and from brain tissue, the relationship of *M. pneumoniae* infection and CNS manifestations is unclear.

In 33% to 76% of patients with *M. pneumoniae,* IgM autoantibody that agglutinates with human erythrocytes at 40°C (cold agglutinins) is evoked (Cassell, 1995), which may result in hemolytic anemia (Cherry, 1993). Significant hemolysis usually occurs only with high titers from cold agglutinin. In general, patients with *M. pneumoniae*-associaled hemolytic anemia have a higher median age than patients without this complication (Cherry, 1993). Other complications possibly related to a hemagglutinin response include paroxysmal cold hemoglobinuria, Raynaud's disease, peripheral gangrene, diffuse intravascular coagulation, thrombocytopenia, and renal failure.

TABLE 3. Respiratory and Nonrespiratory Complications of *M. pneumoniae* Infections[a]

General
Skin rashes
Erythema multiforme
Maculopapular eruptions
Vesicular eruption
Toxic epidermolysis
Erythema nodosum
Arthritis
Glomerulitis
Pulmonary
Adult respiratory distress syndrome
Bronchial asthma exacerbation
Bronchiectasis
Bronchiolitis obliterans
Hyperlucent lung syndrome
Interstitial fibrosis
Lung abscess
Pleuritis
Pneumatocele
Pneumothorax
Pulmonary embolism
Hematologic
Anemia (including hemolytic)
Disseminated intravascular coagulation
Thrombocytopenia
Cardiac
Pericarditis
Myocarditis
Neurologic
Encephalitis
Meningitis, aseptic
Poliomyelitis-like syndrome
Guillain-Barré syndrome
Brain-stem syndrome/cerebellar ataxia
Psychosis
Transverse myelitis
Cerebral infarction
Other
Glomerulonephritis
Nephrotic syndrome
Uveitis

[a]Modified from File et al., 1998; Marrie, 1996.

Cardiac involvement in *M. pneumoniae* is generally considered to be uncommon, but in one prospective study occurred in as many as 4.5% of patients (Farraj et al., 1997; Kenney et al., 1993). Myopericarditis is the most common cardiac manifestation, but hemopericardium and heart block have been described. *M. pneumoniae* has been isolated in pure culture from pericardial and cardiac tissue (Kenney et al., 1993). Polyarthritis is another extrapulmonary manifestation. While arthralgias are common in patients with *M. pneumoniae* infection, arthritis is uncommon. A review by Pönkä (1979) of 1259 patients with *M. pneumoniae* infection identified only 11 patients with associated arthritis.

Diagnosis

A definitive diagnosis of pneumonia caused by *M. pneumoniae* is no frequently obtained (File et al., 1996). The techniques currently used to obtain a laboratory diagnosis of *M. pneumoniae* pneumonia include culture, detection of specific antibodies, and, more recently, direct detection of the organism in respiratory secretions (i.e., DNA sequences by polymerase chain reaction [PCR]) (Table 4; Quinn, 1996; File et al., 1998).

Culture

M. pneumoniae can be isolated from both upper and lower respiratory tract specimens from individuals with pneumonia. Throat swabs, nasopharyngeal swab, throat washes, sputum, tracheal aspirates, bronchoscopy specimens, and lung tissue have all yielded the organism (Lehtomäki et al., 1987; Loo et al., 1991; Nagayama et al., 1987; Hammerschlag, 1995; Quinn, 1996). Because the organism is fastidious, culture media should be inoculated as soon as possible. Culture media dispensed into small vials are often used as transport media. However, culture is not available in most clinical laboratories, and since it requires 1 to 3 weeks to complete, this information is generally not helpful for prospective management of patients.

Serology

Serologic tests that are available in most clinical laboratories include cold agglutinins (nonspecific) and evaluation of specific antibodies by complement fixation (CF) tests or enzyme immunoassay (EIA). Serologic tests have potential drawbacks either because of low sensitivity or requirement of convalescent sera for accurate interpretation. Part of the uncertainty with the laboratory diagnosis of

TABLE 4. Diagnostic Tests for *Mycoplasma pneumoniae*[a]

Test	Specimen	Sensitivity (%)	Specificity (%)	Comments
Culture	Throat or nasopharyngeal swab, sputum, bronchial washings, tissue	>90	50–90	Not routinely available; slow-growing organism (7–10 days for preliminary growth); need DNA probe for speciation
PCR	Throat or nasopharyngeal swab, sputum, bronchial washings, tissue	95	95–99	Not commercially available; available from reference and research laboratories; potentially useful as rapid diagnostic test
Serology	Cold agglutinins	50	<50	Nonspecific; takes several weeks to develop
	Serum, complement fixation, ELISA	75–80	80–90	Paired acute-convalescent sera preferred; takes 4–9 weeks for seroconversion (therefore retrospective); IgM may be present after 1 week but can persist 2–12 months. Diagnostic criteria: Definite: 4-fold increase in titer Possible: IgG = 1:64 (complement fixation); IgM = 1:16 (ELISA)

PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.
[a]Data from Ferraro, 1997; Quinn, 1996.

M. pneumoniae infection is related to the insidious nature of the disease. The patient may not be evaluated for weeks or more after infection. By this time the organisms might not be as readily isolated or the serological response may have already reached an elevated titer, precluding the possibility of meeting the criterion for a current infection of a 4-fold or greater rise in antibody titer.

Elevated cold agglutinins may be an early indication of acute *M. pneumoniae* disease. A titer of 1:64 is supportive of the diagnosis of *M. pneumoniae* but is found in only 30% to 50% of cases (Jacobs, 1993). A positive but low titer may not be due to *M. pneumoniae* because cold agglutinins are also found in several other respiratory diseases, such as infection due to adenovirus, respiratory syncytial virus, mumps virus, and influenzae virus, and several other diseases, including cardiovascular diseases, myelomas, and tropical diseases. Therefore, in the absence of hemolytic anemia, this test appears to have poor clinical utility.

The CF test measures predominantly "early" IgM antibodies to *M. pneumoniae* and, only to a minor extent, IgG antibodies to *M. pneumoniae;* thus the diagnostic value of the CF test may be limited to the initial *M. pneumoniae* infection and may not reveal antibody responses with *M. pneumoniae* re-infection.

The antigen for the CF test is a chloroform-methanol glycolipid extract of *M. pneumoniae* cells. A 4-fold rise in antibody titer of paired sera is considered evidence of recent or current infection. An elevated single titer (i.e., >16) is often considered evidence of probable recent infection, but is not as definitive as a 4-fold or greater rise. The comparability of CF antibodies and culture was evaluated in a detailed 12-year study that included more than 3000 cases of pneumonia (Kenny et al., 1990). The organism was isolated from 360 of 525 patients who showed a 4-fold or greater antibody increase in their paired sera, resulting in a sensitivity of 68%. When persons with titers of greater than 32 but without a 4-fold rise were included, the sensitivity was 58%. In contrast, 4-fold antibody increases were found in 360 of 674 persons with positive cultures. An additional 247 persons with positive culture showed a titer greater than 32, resulting in a combined sensitivity of 90% for serology for the detection of antibody in a culture-positive person.

An EIA measures specific IgM antibodies directed against *M. pneumoniae.* Specific IgM appears in patients approximately 7 days after the onset of symptoms, with peak titers occurring between 4 to 6 weeks (Jacobs, 1993). As with the CF test, titers fall slowly to usually undetectable levels at an estimated 12 to 26 weeks after the onset of symptoms. A rapid IgM assay lest is offered in many laboratories for early serologic evidence of acute infection. However, since *M. pneumoniae*-reactive IgM can persist for 2 months to 1 year after infection (especially in children), detection of specific IgM does not necessarily indicate the time of infection. In general, the absence of specific IgM antibodies in serum collected 10 to 20 days after the onset is relative evidence against pneumonia due to *M. pneumoniae.*

Direct Detection

Efforts to improve the early laboratory diagnosis of infection due to *M. pneumoniae* have involved efforts at direct detection of *Mycoplasma* antigen in respiratory secretions (Marmion et al., 1993; Abele-Horn et al., 1998). Antigen detection by particle agglutination or antigen capture of sputum, throat swabs, or nasopharyngeal aspirates is under development, but is not yet satisfactory for clinical application. DNA amplification using PCR offers a promising lest of potential clinical utility (de Barbeyrac et al., 1993; Falguera et al., 1997; Talkington et al., 1998; Narita et al., 1998). PCR is available through reference laboratories but currently is not easily accessible. There is no kit approved by the U.S. Food and Drug Administration. Nevertheless, several recent studies have evaluated this technique and found it to be useful. One study of 155 patients found that PCR on a single throat swab specimen is a rapid, sensitive, and specific test that may greatly simplify the diagnosis of CAP caused by *Legionella, M. pneumoniae,* or *C. pneumoniae* (Rameriz et al., 1996). *M. pneumoniae* throat swab PCR proved to be more sensitive than acute IgM serology in this study. PCR assays were positive in eight of the nine patients with serologic evidence of *M. pneumoniae* infection (four had

4-fold antibody titer rise and four had positive acute IgM serology).

Therapy

In general, the tetracyclines, macrolides, and fluoroquinolones are active in vitro against *M. pneumoniae* (Table 5) (McCormak, 1993; McMillan, 1998; File et al., 1998). Because *M. pneumoniae* lacks cell walls, these pathogens are not effectively treated with β-lactam agents. In vitro susceptibility testing indicates that *M. pneumoniae* is most sensitive to the macrolides and tetracyclines. In general, the minimum inhibitory concentrations (MICs) are lower for the macrolides than for tetracycline and there is little variability between erythromycin and the newer macrolides (clarithromycin, azithromycin). The MICs of tetracycline and doxycycline are similar. Macrolide-resistant strains have been described but appear to be uncommon; resistance to tetracycline has not been encountered (McCracken, 1986; McMillan, 1998). In an animal model of *Mycoplasma* infection, both erythromycin and tetracycline inhibited, but did not kill, *M. pneumoniae.* The data from this model indicated that early treatment with tetracycline or erythromycin after inoculation delayed, but did not prevent, the development of pneumonia.

TABLE 5. In Vitro Activity of Various Antibiotics against *Mycoplasma pneumoniae*[a]

Drug	*M. pneumoniae* MIC (μg/mL)
Erythromycin	<0.002–0.004
Tetracycline	0.25
Doxycycline	0.25
Azithromycin	<0.001–0.004
Clarithromycin	<0.004–0.125
Ciprofloxacin	1–8
Ofloxacin	1–2.0
Levofloxacin	0.5
Sparfloxacin	0.06–0.25
Grepafloxacin	0.06–0.25
Trovafloxacin	0.12–0.25

MIC, minimum inhibitory concentration.
[a]From Renaudin & Bébéar, 1990; Hammerschlag, 1995; Kenny & Cartwright; 1996; File et al., 1997; Ridgeway et al., 1997; McMillan, 1998.

Isolates of *M. pneumoniae* are also susceptible to the fluoroquinolones, although MICs are not as low as for the macrolides or tetracyclines. The newer fluoroquinolones with enhanced activity against *S. pneumoniae*—levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin—are more active in vitro against *M. pneumoniae* than prior fluoroquinolones.

Therapy of *M. pneumoniae* has been the subject of some conjecture. A prevailing view is that it really does not matter whether antibiotics are given for most infections since the mortality is low, infections are often self-limiting, and there may be ambiguity of diagnosis (prompt etiologic confirmation is difficult to establish). However, studies have shown that treatment reduces the morbidity of pneumonia and shortens duration of symptoms. In a large placebo-controlled clinical trial of antimicrobial agents for therapy of *M. pneumoniae* pneumonia, Shames et al. (1970) studied 317 military recruits who received one of six different antibiotics (Table 6). Forty-three trainees with serologically proven *M. pneumoniae* received either no therapy or penicillin G, which served as controls. All antibiotics were more effective in reducing clinical illness as well as resolving abnormalities on chest radiograph than no therapy or therapy with penicillin G. These investigators also evaluated the effect of therapy on shedding of *Mycoplasma* in respiratory secretions. Cultures were positive in a variable number of patients at the beginning of therapy as well as after therapy. The clinical and radiographic responses to therapy were similar, regardless of *Mycoplasma* recovery after completion of therapy. Other studies evaluating erythromycin or tetracycline have found that *M. pneumoniae* may persist in respiratory secretions despite good clinical response to therapy (Smith et al., 1967). Cultures may remain positive for weeks to months even after symptoms have resolved (McMillan, 1998).

In a randomized controlled treatment of clarithromycin versus erythromycin in 260 children with CAP, Block et al. (1995) observed that 69 (29%) had evidence of *M. pneumoniae* (most detected by PCR or culture). Treatment with clarithromycin or erythromycin eradicated *M. pneumoniae* in both treatment groups. Azithromycin has also been found to be effective against *M. pneumoniae* in recent studies and may allow a shorter duration

TABLE 6. Clinical Effect of Therapy for *Mycoplasma pneumoniae* Pneumonia[a]

Drug	No. of patients treated	Days febrile (mean)	Days of abnormal chest x-ray (mean)	No. of positive cultures pretherapy	Total cultured[b] after therapy (%)
Controls	39	4.2	14.8	12/19 (63)	1/3 (33)
Demedocycline	26	1.8	6.7	28/72 (39)	2/29 (7)
Tetracycline	89	2.4	9.3	8/37 (22)	2/37 (5)
Erythromycin stearate	76	2.4	7.2	32/89 (40)	2/27 (7)
Erythromycin ethyl succinate	43	3.0	11.3	11/25 (44)	4/22 (18)

[a]Data from Shames et al., 1970.
[b]Patients without positive culture had diagnosis confirmed by serologic methods.

of therapy (Gregory et al., 1997; Plouffe et al., 2000).

The newer fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin) are more active in vitro than ciprofloxacin against *M. pneumoniae* and have been shown to be effective in early trials in *M. pneumoniae* infections (Bébéar et al., 1993; Plouffe et al., 1996; File et al., 1997). These studies have predominantly relied on serologic means of diagnosis but have shown good efficacy.

Recommendations for therapy of *M. pneumoniae* pneumonia are included in Table 7. The recommended duration of therapy for adults for *M. pneumoniae* pneumonia is 10 to 14 days of doxycycline or erythromycin. Clarithromycin 1 g/day for 10 days has been shown to be effective as has azithromycin 1.5 g administered over 5 days. The studies of fluoroquinolones to date indicate that a schedule of 7 to 10 days is appropriate for the treatment of *M. pneumoniae* infection. Choice of regimens depends on patient compliance, tolerance, and cost. Further prospective studies using microbiologic techniques may provide additional information concerning the best therapeutic regimen for treatment of respiratory infections caused by *M. pneumoniae.*

It must be acknowledged that most patients with *M. pneumoniae* infection are treated empirically. Recently published guidelines for the treatment of CAP suggest that empiric therapy should include antimicrobial agents effective against *M. pneumoniae* and other atypical pathogens as well as the standard pyogenic common causes (*S. pneumoniae, H. influenzae*) (Niederman et al., 1993; Bartlett et al., 1998). Based on present data, the decision to use therapy specific for *M. pneumoniae* in the management of patients with CAP will depend to a great extent on clinical judgment as well as the recommendations of various guidelines.

The role of therapy other than antimicrobials

TABLE 7. Antimicrobial Therapy for *Mycoplasma pneumoniae* Pneumonia

Antibiotic	Oral dose	Duration
Erythromycin	Adults: 1–2 g/day divided 4 times a day	10–14 days
	Children: 40 mg/kg/day divided 4 times a day	10–14 days
Clarithromycin	Adults: 250–500 mg/day divided twice a day	10 days
	Children: 15 mg/kg/day divided twice a day	10 days
Azithromycin	Adults: 500 mg/day divided twice a day × 1 day, followed by 250 mg/day × 5 days	5 days total
	or 500 mg/day	3 days total
	Children: 10 mg/kg/day divided twice a day × 1 day, followed by 5 mg/kg/day × 4 days	5 days total
Tetracycline	1–2 g/day divided 4 times a day	10–14 days
Doxycycline	200 mg/day divided 4 times a day	10–14 days
Levofloxacin	500 mg/day	7–14 days
Sparfloxacin	400 mg (first day), then 200 mg/day	7–14 days
Gatifloxacin	400 mg/day	7–14 days
Moxifloxacin	400 mg/day	7–14 days

in the management of pulmonary complications and the extrapulmonary manifestations of *M. pneumoniae* infection has not been well defined. While immune mechanisms may have a role in such conditions as hemolytic anemia and CNS involvement, the role of corticosteroid therapy remains unresolved (Koshiniemi et al., 1997; McMillan, 1998). Based on favorable results from anecdotal reports and small series of patients, corticosteroid therapy has been recommended for complications such as bronchiolitis obliterans and hemolytic anemia (Cherry, 1993; Chan & Walsh, 1995; Llibre et al., 1997).

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