85 Mycoplasma Infection

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Etiology

Mycoplasma pneumoniae, originally called the Eaton agent, was first isolated from a sputum culture in a patient with atypical pneumonia in 1944. Twenty years later, it was ultimately identified to be a *Mycoplasma* not a virus as once thought. Mycoplasmas are the smallest self-repliacting prokaryotes with a size of approximately 120–150 nm. These organisms cannot be seen by light microscopy nor do they produce visible turbidity in liquid growth media.

Like other bacteria in its Mollicutes class, Mycoplasmas lack the gene necessary to synthesize peptidoglycan cell walls. The absence of a cell wall explains its pleomorphic phenotype, inability to stain with Gram stain, and its resistance to antibiotics that interfere with cell-wall synthesis such as beta-lactams. While Mycoplasmas are found in many animals and plants, humans are the only known host for *M. pneumoniae* infection.

For many years, it was believed that *M. pneumoniae* infections were self-limited, confined to the respiratory tract, and involved only adolescents and young adults. Over time, much has been learned about this pathogen, its epidemiology, pathogenesis, and variety of clinical manifestations.

Epidemiology

M. pneumoniae, an exclusively human pathogen, is a frequent respiratory pathogen causing up to 40% of outpatient pediatric community-acquired pneumonia and 12–25% of lower respiratory-tract infections in hospitalized children. Once thought to infect primarily adolescents and young adults, recent literature suggests increasing infection in younger children. Worldwide, the incidence of *M. pneumoniae* infection is highest in children aged 5–9 years. However, a study of community-acquired pneumonia in children in Korea found that children less than 5 years accounted for over 44% of the 568 *M. pneumoniae* cases. Infants have also been documented to have *M. pneumoniae* infection, however, rarely.

M. pneumoniae occurs endemically and epidemically worldwide and throughout the year, with peaks in the summer and early fall months when the frequency of other respiratory pathogens is low. Community epidemic infections can be seen in 3–5 year cycles, with each epidemic lasting a few months. The 2–3 week incubation period in combination with asymptomatic nasopharyngeal carriage that persists for months beyond the initial infection likely contribute to these lengthy periods. During these epidemics, the frequency of infection can be 5–20 times greater than during the endemic periods. As *M. pneumoniae* is transmissible by respiratory droplets during close contact with a symptomatic person, these outbreaks tend to occur in closed populations such as military bases, colleges, and summer camps.

Mycoplasma infection elicits protective immunity; however, it is short lived, and reinfections throughout life are common. Naturally acquired infection in which pneumonia develops results in longer protective immunity than mild or asymptomatic infection.

Pathogenesis

Respiratory disease caused by *M. pneumoniae* is dependent on the close association between the host respiratory epithelium and the pathogen. This cytadherence process, considered a major virulence factor of this organism, is essential to colonization and infection as alteration of any of these proteins results in the organism's inability to cause infection. Subsequently, the immune response elicited, while responsible for much of the disease process, does not effectively clear the organism or produce long-term immunity.

M. pneumoniae enters the respiratory tract via inhalation of aerosolized droplets spread by symptomatic close contacts. The pathogen, with the help of P1 adhesion protein and accessory proteins, attaches to the ciliated epithelium and is thus protected from the host's mucociliary clearance mechanism. Close contact between host cell and pathogen allows for the pathogen's release of hydrogen peroxide and superoxide radicals directly onto

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the cell, which in combination with the toxic oxygen molecules produced by the host induces oxidative stress on the respiratory epithelium causing local disruption and cytotoxicity. Clinically, this damage to the respiratory tract manifests as a prolonged and irritating cough.

M. pneumoniae then reaches the base of a ciliated cell in the lower respiratory tract, where multiplication of organism occurs. Here, Mycoplasma is opsonized by complement and antibody and then phagocytosed by activated macrophages drawn to site of infection by chemotaxis, inducing a cytokine release. CD4+ T cells and B cells infiltrate the lung resulting in lymphocyte proliferation, antibody production, and further cytokine production, including interleukins, interferons, and tumor necrosis factor, and thus the development of pulmonary infiltrates seen on radiologic imaging. The stronger the immune response and cytokine production, the more severe the clinical picture develops.

Extrapulmonary manifestations of Mycoplasma infection occur by a variety of mechanisms, involving both immune-mediated processes (including autoimmunity, cytokine production, and the development of immune complexes) and direct invasion with dissemination. The presence of cross-reactive antibodies results in autoimmune reactions leading to neurological and hematologic presentations specifically encephalitis, Guillain–Barre syndrome (GBS), cranial and peripheral neuropathies, and autoimmune hemolytic anemia. Autoantibodies to ganglioside GM1 and galactrocerebroside have been implicated in the development of *M. pneumoniae* associated GBS, while those recognizing the I antigen of human red blood cells leads to development of cold agglutinins, previously used as a diagnostic tool in identifying Mycoplasma infection. These above-mentioned pathways are not exclusive and, as a result of the multiple pathogenic mechanisms, clinical presentation can be complex with or without respiratory symptoms.

Pathology

There are currently no cases describing histopathology of Mycoplasma infection in the pediatric population. Histopathologic examination has been reported in a few adult cases, animal models, and tracheal organ cultures, revealing lesions of the epithelial lining of the mucosal surfaces, ulceration, and destruction of the ciliated epithelium of the bronchi and bronchioles, bronchial and bronchiolar edema, and bronchiolar and alveolar infiltrates of macrophages, lymphocytes, neutrophils, plasma cells, and fibrin. Reports have also described Type II pneumocyte hyperplasia, diffuse alveolar damage, fibrinous exudates in the pleura, and lung abscesses. In fatal cases, desquamative interstitial pneumonia with focal alveolar disease and bronchiolitis obliterans have been seen.

Clinical Manifestations

Respiratory Tract

M. pneumoniae the most common pathogen causing an "atypical pneumonia," is known to infect both the upper and lower respiratory tract. The illness is usually gradual in progression over days to weeks, although sudden onset of dyspnea and cough has been reported. Three to ten percent of patients infected with *M. pneumoniae* go on to develop pneumonia.

Children present most commonly with fever and cough. The cough initially is dry and nonproductive but may develop into a mucopurulent cough, occasionally with blood streaked sputum. Children with Mycoplasma pneumonia are more likely to have a have a history prolonged fever that does not respond to beta-lactam antibiotics than those with pneumonia of other infectious etiology. Other symptoms include sore throat, headache, lethargy, chills, myalgias, rash, and a protracted cough which may become paroxysmal. Younger children tend to present with more rhinorrhea, wheezing, vomiting, and diarrhea, whereas older children and adolescents complain about sinus fullness and ear pain and are more likely to develop bronchopneumonia. The clinical presentation of Mycoplasma respiratory infection can mimic that of both respiratory viruses and/or pertussis making the diagnosis more difficult.

Physical-exam findings are dependent on the site of infection and, early in illness, can include non-exudative pharyngitis, myringitis, and cervical adenopathy. The etiology of bullous myringitis, thought to be pathognomonic of *M. pneumoniae*, has been shown to be a variety of organisms with Mycoplasma being only a rare cause. As the illness progresses over days to a week, the fever and upper respiratory symptoms resolve, and the lower respiratory findings become more prominent including tachypnea, scattered rales, ronchi, and/or wheeze on auscultation of the chest. The presenting symptoms usually resolve within 2 weeks; however, symptom resolution can take months.

Chest x-rays are usually abnormal in patients with Mycoplasma pneumonia; however, the findings are variable and not specific for *M. pneumoniae*. Lobar consolidation (typically unilateral and involving lower lobes) is a common finding as well as bilateral interstitial changes.

Hyperinflation, bronchial thickening, and hilar lymphadenopathy can also be seen. Parapneumonic effusions can be seen in 4–20% of patients. Improvement of radiographic findings lags behind clinical improvement by months.

Extrapulmonary Manifestations

While the respiratory tract may be the most common site infected by *M. pnueumoniae*, any organ system can be involved. Twenty five percent of hospitalized patients with Mycoplasma infection have extrapulmonary manifestations. These symptoms can occur before, during, after, or in the absence of respiratory symptoms. Although the pathogenesis of extrapulmonary manifestations is unclear, it is hypothesized to include direct invasion and/or autoimmune processes.

Table 85.1 lists the extrapulmonary complications associated with *M. pneumoniae* infection. The most common of the extrapulmonary manifestations are dermatologic, affecting 25% of infected patients, and neurologic, seen in 7–10% of hospitalized patients with Mycoplasma infection. The skin presentations can be, but are not limited to urticarial, vesicular, or maculopapular. *M. pneumoniae* is one of the most common infectious agents associated with Stevens–Johnson syndrome both with and without rash. Central nervous system (CNS) manifestations most commonly are encephalitis, meningoencephalitis, polyradiculitis, and aseptic meningitis. *M. pneumoniae* encephalitis is more frequent in children than in adults, and this pathogen should be on the differential diagnosis of patients with CNS disease, especially if associated with pneumonia.

Table 85.1
Extrapulmonary manifestation with *Mycoplasma pneumoniae* infection

Organ system	Clinical manifestation
Dermatologic	Urticarial or vesicular rash
	Erythematous maculopapular rash
	Stevens–Johnson syndrome
	Erythema multiforme
Central Nervous System	Encephalitis, Meningoencephalitis
	Aseptic meningitis
	Cerebellar ataxia
	Cranial and peripheral neuropathy
	Transverse myelitis
	Guillan–Barre syndrome
	Confusion
	Psychosis
Ocular	Optic neuritis
	Diplopia
	Conjunctivitis
	Retinitis
	Anterior uveitis
	Retinal hemorrhage
	Iritis
Hematologic	Hemolytic anemia
	Intravascular coagulation
Gastrointestinal	Vomiting
	Diarrhea
	Mild elevation of hepatic enzyme
	Pancreatitis
Cardiac	Heart failure
	Myocarditis
	Pericarditis
	Pericardial effusion
Renal	Glomerulonephritis
	IgA nephropathy
Bone/Joint/Muscle	Myalgias
	Arthralgias

Special Circumstances

Children with underlying conditions, such as sickle-cell disease, Down syndrome, and immunosuppression, are more likely to develop severe Mycoplasma infection with fulminant pneumonia and joint infection. *M. pneumoniae* infection has been associated with acute chest syndrome and multilobar infiltrates with large bilateral pleural effusions in patients with sickle-cell disease.

There is little published data describing *M. pneumoniae* infection in the pediatric HIV population. Recently, a study in India evaluated 90 HIV seropositive children who were hospitalized with acute respiratory symptoms. IgM antibodies specific for *M. pneumoniae* were seen in 32% of these children, with the majority of these patients between 6 and 9 years of age. Cough and fever were the most common presenting symptoms, in combination with headache, joint pain, dyspnea, sore throat, and hemoptysis. Almost all of these children were anemic and many had elevated hepatic enzymes, a side effect seen with many anti-retrovirals as well.

Diagnosis

Growing Mycoplasma in culture is difficult, labor intensive, and expensive. Special care is required to meet the complex nutritional needs to achieve growth, which can take up to 4 weeks. The sensitivity of culture is low at 61% when compared to PCR. As Mycoplasma can persist in the nasopharynx for months after the initial infection, isolation of the pathogen does not necessarily implicate it as the etiology of the current illness. Therefore, culture for Mycoplasma is not recommended for routine diagnosis.

Bedside testing of cold agglutinins was once the primary diagnostic tool for Mycoplasma infection. Cold agglutinins are an early nonspecific IgM antibody against the "I" antigen of the human erythrocyte. These autoantibodies are most active at 4°C. To test for cold agglutinins, the patient's blood would be drawn into a tube containing anticoagulant. The tube would be placed in ice water for 30 s to 5 min and then examined for agglutination. The strength of the agglutination correlates with the severity of disease. Cold agglutinins can be seen in half of patients infected with *M. pneumoniae*; however, false positives can be seen in children with lymphoproliferative disorder, infectious mononucleosis, influenza, and adenovirus infections. Lack of sensitivity, specificity, and standards render this method impractical in clinical situations.

There are several serological tests of *M. pneumoniae*, including complement fixation, passive agglutination, immunofluorescent antibody assays, and enzyme immunoassays (EIAs) which are the most commonly used. Complement fixation, the first serological method developed for *M. pneumoniae*, measures early IgM response without differentiating between the antibody classes. Since it is now known that Mycoplasma antibody can persist for months to years, this differentiating between antibody classes is important in distinguishing acute infection from old infection. EIAs have become more widely used for *M. pneumoniae* detection. The sensitivity of EIAs in *M. pneumoniae* detection is higher than that of culture and is even comparable to that of PCR.

Serologically, the diagnosis is made retrospectively with collection of acute and convalescent sera 2–4 weeks apart to show evidence of seroconversion. A fourfold increase in antibody titer between acute and convalescent titers or a single anti-Mycoplasma antibody titer of $>$1:128 is diagnostic of acute Mycoplasma infection. Similar to the time needed for culture, the need for acute and convalescent titers is a limitation in acute management, and empiric treatment should be given based on clinical suspicion.

New molecular-based testing such as PCR has been increasingly used in Mycoplasma detection. PCR allows for same day results and detection of Mycoplasma from body fluids, such as blood and CSF. While PCR has high sensitivity, a positive PCR result from a patient with a negative culture without respiratory disease is difficult to interpret since this may represent persistence of pathogen without infection or asymptomatic carriage.

Differential Diagnosis

Respiratory infection caused by *M. pneumoniae* commonly shares clinical features with respiratory viruses such as influenza, adenovirus, parainfluenza virus, respiratory syncytial virus, and human metapneumovirus. Similarly, other bacteria and atypical organisms should be considered in the differential diagnosis, including *Streptococcus pneumoniae*, *Haemophilus influenzae, Staphylococcus aureus*, and *Chlamidyophila pneumoniae.* In patients who present with protracted, paroxysmal cough, the diagnosis of pertussis should be considered.

Treatment

When *M. pneumoniae* infections were first described, antibiotic therapy was thought to be unnecessary as these illnesses were mild and self-limiting. Over time, antibiotics have been shown to decrease duration of both fever and respiratory symptoms. As it is difficult to obtain a microbiologic result at the time of the patient visit, empiric therapy should be started with clinical suspicion of Mycoplasma associated lower respiratory tract infection.

Beta-lactams and glycopeptides, commonly used to treat community-acquired pneumonia, are ineffective against Mycoplasma since this organism lacks a cell wall. Macrolides are currently the recommended treatment of choice for infection with *M. pneumoniae*. Azithromycin and clarithromcyin are clinically as effective as erythromycin and are better tolerated, given only once or twice a day, and require shorter treatment duration in the case of azithromycin. Fluoroquinolones and tetracyclines are also effective antimicrobial agents and, unlike macrolides, there have been no reported Mycoplasma resistance to these classes. However, due to the significant toxicities associated with these medications in the pediatric population, macrolides remain the drugs of choice. While antibiotic therapy may decrease clinical symptoms, they do not eradicate the organism and asymptomatic carriage may persist and subsequent reinfection may occur.

Macrolide resistant strains of Mycoplasma contain a mutation in the 23S rRNA gene decreasing the affinity of these medications for the ribosomes. First described in Europe, clinical resistance to macrolides has been increasing worldwide over the past decade. Rates of macrolide resistance have ranged from a few case series in the United States to 3% in Germany and 13% in Japan to 69% in a study in China. Children with macrolide resistant Mycoplasma infection were found to have longer fever duration than those with infection with a susceptible organism.

There is little data available regarding the treatment of extrapulmonary manifestations of *M. pneumoniae*. The pathogenesis of these clinical presentations is unclear and thought to be due to direct invasion and dissemination and/or an autoimmune response. Therefore, treatments have included antibiotics, steroids, as well as plasmapheresis and intravenous immunoglobulin. There currently have been no controlled studies evaluating these treatment options with extrapulmonary systems and no consistent studies showing any benefit. It is reasonable, since Mycoplasma can cause severe disseminated disease, to start antibiotics in patients with central nervous system disease, hemolysis, or cardiac disease when infection with *M. pneumoniae* is suspected.

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