Mycoplasma pneumoniae Infections in Childhood

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IMPORTANCE IN COMMUNITY-ACQUIRED RESPIRATORY INFECTIONS

Mycoplasma pneumoniae is responsible for up to 40% of community-acquired pneumonias in children over 5 years of age. Community-acquired pneumonias due to M. pneumoniae may increase several fold during epidemics that occur every 4–7 years, believed to be due to waning of herd immunity and introduction of new subtypes into the population. The peak incidence reported in Scotland during the recent European epidemic was 14.2 per 100,000 population.1

Extrapulmonary manifestations involving every organ system can occur and may be due to spread of infection or autoimmune mechanisms. Perhaps the most common is the development of an autoantibody to the I blood group antigen (cold agglutinins), which can produce a rapidly evolving hemolytic anemia. Neurologic manifestations can also be prominent, including Guillain-Barré syndrome and acute demyelinating encephalomyelitis. A syndrome of severe mucocutaneous involvement resembling Stevens-Johnson syndrome occurs in some individuals. Numerous case reports and small series document the ability of the organism to cause septic arthritis, particularly in individuals with hypogammaglobulinemia, and the organism may also be responsible for some cases of chronic arthritis in children and adults.

PATHOGENESIS AND IMMUNE RESPONSE

Following inhalation, M. pneumoniae attaches to ciliated cells of the respiratory epithelium using a specialized attachment (CaRDS) toxin, binds to surfactant protein A and enters host cells by clathrin-mediated endocytosis.3 CARDS toxin produces ciliostasis and nuclear fragmentation and stimulates production of proinflammatory cytokines and an acute cellular inflammatory reaction, leading to airway damage. The amount of toxin produced is controlled by environmental conditions and correlates with disease severity.3 Intracellular localization, described in tissue culture models, may be responsible for protecting the organisms from antibodies and antibiotics, as well as contributing to establishment of persistent infections.3 Immunomodulation of the host immune response enables establishment of persistent infections and causes autoimmune phenomena. Many clinical manifestations of acute infection as well as extrapulmonary complications are due to immunopathologic and inflammatory effects produced by the host, rather than the organism itself. Various surface lipoproteins stimulate production of interleukin-6, tumor necrosis factor alpha and neutrophil infiltration. M. pneumoniae also stimulates B and T lymphocytes and induces formation of autoantibodies that react with a variety of host tissues. M. pneumoniae may be opsonized by complement or antibodies. Macrophages become activated and undergo chemotactic migration to the site of infection. Neutrophils, CD4+ T lymphocytes, B lymphocytes and plasma cells then infiltrate the lung.

A strong humoral immune response produces antibodies to several immunogenic M. pneumoniae proteins and lipids following infection. IgM may be detected after about 1 week of illness, peaking at 3–6 weeks, followed by a gradual decline in children older than 6 months of age. IgG typically follows the IgM response 2 weeks later. IgM can sometimes persist for several weeks to months, or may not occur at all, especially in middle-aged or older adults who have had multiple previous infections. Antibody production may be absent if the patient is immunocompromised. Surface antigen variation and rearrangement appears to be an important factor related to lack of protective immunity, which can lead to repeated M. pneumoniae infections over time.

ROLE IN ASTHMA

Evidence is accumulating that the microbiome of patients with asthma differs from nonasthmatic individuals in having higher numbers and diversity of resident bacteria and in the predominant types of bacteria present. There are 2 main questions relating to a possible role of M. pneumoniae in asthma: the first relating to a role M. pneumoniae in chronic airway hyperreactivity and the second to a role in acute asthma exacerbations. Stronger evidence exists for a role for M. pneumoniae in chronic asthma than as a common cause of acute exacerbations. In many older studies, particularly those investigating acute exacerbations, diagnosis hinged entirely upon single serologic results. This approach is potentially flawed because low levels of IgG antibody are present in the general population and IgM antibodies can be detected in some individuals for months or even years following infection. The best strategies for convincing microbiologic diagnosis and confirming the role played by M. pneumoniae in asthma are culture, polymerase chain reaction (PCR) with appropriate controls (preferably testing for two separate target genes), acute and convalescent sera showing at least a 4-fold rise in antibody titer or a combination of these approaches.

Studies using nucleic acid amplification tests (NAATs) and antigen capture assays for the CARDS toxin have strengthened the case for a role of M. pneumoniae in chronic asthma. Martin et al4 reported that 23 of 55 chronic stable adult asthmatics (42%), all serologically negative, were positive for M.
**Pneumonia** in upper or lower airway by PCR, compared with 1 of 11 controls (9%). In a similarly designed follow-up study designed to test for response to macrolide therapy and which did not include nonasthmatic controls, Sutherland et al. found only 13% PCR positivity. Using PCR to detect the gene for the CARD5 toxin in 64 adults with treatment-resistant asthma, Peters et al. found a high prevalence of *M. pneumoniae* (52%) in this population, most of whom were serologically negative. However, there was no control group in this study with which we could make comparisons. In a pediatric study by the same group that did include nonasthmatic controls, *M. pneumoniae* was detected in 64% of patients with acute asthma, 65% with refractory asthma and pneumonias was detected in 64% of patients with pneumonia who were culture- and/or PCR-positive for *M. pneumoniae* and who were also positive for IgM. A combination of IgM or IgA and PCR has been suggested as an optimum diagnostic approach, but would add considerable cost to laboratory testing.

NAATS can detect *M. pneumoniae* earlier than serology because development of antibodies may require several days. NAATs performed on a nasopharyngeal or throat swab can provide results the same day the sample is received in a diagnostic laboratory. Various gene targets and assay formats are now available commercially in Europe and the United States in either monoplex or multiplex form, but there have been very few side-by-side comparisons to determine whether one assay format or gene target is better than another. Many evaluations have compared NAATs with culture or serology as a reference method and predictably yielded disparate results because NAATs are inherently more sensitive. Limited evaluations of commercial PCR assays sold in Europe have shown that they function with comparable sensitivity and specificity to non-commercial assays.

A pediatrician who has access to a laboratory that offers NAAT for *M. pneumoniae* should inquire about the nature of the test, the gene target, how the test was validated and whether the laboratory subscribes to any type of external proficiency testing or blinded specimen exchange to verify the quality of results. Performing NAATs on children who do not exhibit typical manifestations suspicious for mycoplasmal infection is not recommended.

**Diagnostic Methods**

Most *M. pneumoniae* infections in children are amenable to management on an outpatient basis, so physicians often rely on clinical suspicion and provide empiric treatment. However, a microbiologic diagnosis should be sought if illness is sufficient to warrant hospitalization, if there is unsatisfactory clinical response to initial antimicrobial therapy, if there are significant underlying comorbidities or immunosuppression that would make severe and disseminated disease more likely and if significant extrapulmonary symptoms are present. Due to the prolonged turnaround time, specialized expertise required, limited availability and poor sensitivity, culture is rarely performed. Serology was the primary means for diagnosis for many years. Enzyme immunoassays (EIAs) are the most widely used serologic methods in many countries, although other methods such as particle agglutination assays and immunofluorescence are also used. EIAs can be performed with very small volumes of serum to provide isotype-specific data for IgM, IgG and IgA. Rapid EIAs for IgM have been developed for detection of acute infection using a single serum specimen. However, one such EIA had a sensitivity of only 31.8% when a single serum sample was analyzed from Japanese children with pneumonia, increasing to 88.6% when paired acute and convalescent sera were analyzed. Evaluations of commercial EIAs and particle agglutination assays using PCR as a reference have found that most assays have problems with sensitivity and specificity, especially if only a single specimen is analyzed. IgA may rise more quickly and decline sooner than IgM or IgG. However, a recent evaluation of a commercial IgA assay in our laboratory detected no IgA-positive specimens from patients with pneumonia who were culture- and/or PCR-positive for *M. pneumoniae* and who were also positive for IgM. A combination of IgM or IgA and PCR has been suggested as an optimum diagnostic approach, but would add considerable cost to laboratory testing. NAATs can detect *M. pneumoniae* earlier than serology because development of antibodies may require several days. NAATs performed on a nasopharyngeal or throat swab can provide results the same day the sample is received in a diagnostic laboratory. Various gene targets and assay formats are now available commercially in Europe and the United States in either monoplex or multiplex form, but there have been very few side-by-side comparisons to determine whether one assay format or gene target is better than another. Many evaluations have compared NAATs with culture or serology as a reference method and predictably yielded disparate results because NAATs are inherently more sensitive. Limited evaluations of commercial PCR assays sold in Europe have shown that they function with comparable sensitivity and specificity to non-commercial assays.

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**Antimicrobial Resistance and Treatment**

Macrolides have been the treatments of choice for *M. pneumoniae* infections in children, and resistance was uncommon before 2000. Since then, macrolide-resistant *M. pneumoniae* (MRMP) caused by point mutations in domain V of 23S rRNA has emerged in Asia and spread into Europe and North America. Recent surveillance studies conducted in pediatric populations within the past 5 years have documented resistance rates of 46–93% in Japan, 69–97% in China, 12–23% in Taiwan, 61% in South Korea, 30% in Israel, 9.8% in France and 8.2% in the United States. Typing of clinical isolates of MRMP by multilocus variable-number tandem repeat analysis has not revealed any link between a particular multilocus variable-number tandem repeat analysis type and macrolide resistance, confirming absence of a particular emerging macrolide-resistant clone. Emergence of resistance due to selection pressure during macrolide therapy in individual patients has been documented in children in France, Italy and Israel. While there are no apparent differences in initial presentation that can be used to distinguish a child with MRMP, several investigations have shown that when MRMP occurs, it is clinically significant resulting in prolonged fever, coughing, longer hospital stays or more pronounced chest radiograph changes when compared with children with infections caused by susceptible strains. Successful treatment of MRMP has been achieved with minocycline, doxycycline, tigecycline or fluoroquinolones. Normally these drug classes are not used in children, but in the case of MRMP, there are no other realistic alternatives. In Asia, where resistance rates are extremely high, clinicians should consider using an alternative to macrolides as initial treatment of suspected or confirmed *M. pneumoniae* infection. However, in Europe and North America where resistance is still much less common, macrolides should still be considered the first line treatment, but with careful follow up and consideration for change to another drug class if clinical response is unsatisfactory. In our diagnostic laboratory, every real-time, PCR-positive specimen is subjected to a second PCR reaction to detect the 23S rRNA mutations and both results are reported at the same time, so clinicians have additional information to guide treatment decisions. Continued surveillance for MRMP at local and national levels is extremely important. Clinicians must be aware of this emerging problem and the potential for macrolide treatment failures when managing these infections in their patient populations.

**References**


