Mycoplasma Pneumonia in Children and Adolescents

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Practice Gap

Mycoplasma pneumoniae is a frequent cause of respiratory infections, including community-acquired pneumonia, in school-age children. However, as the science surrounding the diagnosis of this pathogen improves, our knowledge of its epidemiology, including asymptomatic carriage, and the management of this disease is evolving.

Objectives

After completing this article, readers should be able to:

1. Understand the microbiology and epidemiology of *Mycoplasma pneumoniae* infection.
2. Describe the variable clinical presentation of *M pneumoniae* infection and extrapulmonary manifestations.
3. Understand the difficulties associated with diagnosing infection with *M pneumoniae* and current recommendations for diagnosis.
4. Appropriately treat patients with suspected *Mycoplasma* infection.

CLINICAL CASE

A 9-year-old girl presents to her pediatrician with a fever, decreased energy, and a cough for 10 days. She was initially evaluated 4 days ago when she had rhinorrhea, a cough, and decreased energy over the previous week. Her examination at that time was notable only for a mildly erythematous posterior oropharynx and nasal discharge. She was diagnosed as having a viral upper respiratory tract infection, and supportive care measures were recommended. Since that visit, her cough is more persistent and she has developed fevers. On examination her temperature is 100.8°F (38.2°C), heart rate is 100 beats/min, respiratory rate is 40 breaths/min, and oxygen saturation is 90% on room air. She is generally well-appearing. Her physical examination is remarkable for an erythematous posterior oropharynx, nasal discharge, and bilateral diffuse crackles on auscultation of her lungs. What is the next step in diagnosis and management?

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ABBREVIATIONS

CAP	community acquired pneumonia
EM	erythema multiforme
FDA	Food and Drug Administration
MIRM	*Mycoplasma pneumoniae*–induced rash and mucositis
PCR	polymerase chain reaction
SJS	Stevens-Johnson syndrome

MYCOPLASMA DEFINED

Microbiology

Mycoplasma pneumoniae is a tiny, pleomorphic bacteria belonging to the class Mollicutes and is the smallest self-replicating bacteria pathogenic in humans, its

only known host. *M pneumoniae* is unique in having no cell wall, which leads to its pleomorphism and inability to be seen on a Gram-stain. (1)

Epidemiology

M pneumoniae is a common cause of both upper and lower respiratory tract infections in children. Up to 10% of children who are infected will develop pneumonia. *M pneumoniae* is a common cause of pneumonia in school-age children, accounting for up to 20% of cases. (2) It is uncommon in preschool-age children because pneumonia in this age group is typically due to viral etiologies. The incubation period is 1 to 4 weeks, although most commonly 2 to 3 weeks. (2) *Mycoplasma* is easily transmissible among members of the same household and is spread by direct droplet contact. (1)

This clinical prevalence may be overestimated due to asymptomatic carriage. (1)

One study from the Netherlands performed *M pneumoniae* polymerase chain reaction (PCR) on a group of asymptomatic healthy children (n = 405) and a group of children with symptoms of a respiratory tract infection (n = 321) aged 3 months to 16 years. The *M pneumoniae* PCR was positive in 21.2% of the asymptomatic children and in 16.2% of the symptomatic children ($P = .11$). Follow-up of a smaller group of these children found that by 1 month most children in both groups were PCR negative; no children remained positive after 3 months. (3) Other studies examining asymptomatic carriage have found variable rates of detection.

Although *M pneumoniae* infections can occur year-round, they are most commonly detected in the winter months. Epidemics of *M pneumoniae* infection occur every 3 to 7 years in the United States, starting most commonly in the fall; however, they may not be noticed immediately given that testing is not routinely performed (1) and because symptoms are fairly nonspecific. Outbreaks commonly occur in closed settings such as schools, camps, nursing homes, and military bases. (2) Carriage of the organism in the upper respiratory tract remains after antimicrobial treatment, which may contribute to prolonging outbreaks. (1)

CLINICAL PRESENTATION OF *M PNEUMONIAE* INFECTION

Respiratory Tract Manifestations

M pneumoniae primarily infects the upper respiratory tract. Cough is the most common presenting symptom and is present in 90% to 100% of patients. Onset of illness is gradual, with nonspecific symptoms such as fever and malaise. This presentation worsens over several days, with findings of pneumonia developing at approximately days 6 to 10 in 3% to 10% of patients. (4) The cough can last for 3 to 4 weeks and may or may not be associated with wheezing. Patients may also report headache (60%–84%), sore throat (6%–59%), nasal symptoms (2%–40%), and ear pain (2%–35%). (5) The presence of chest pain increases the likelihood of infection due to *Mycoplasma* twofold. (6)

Findings on physical examination are nonspecific and difficult to distinguish from other respiratory tract infections. Patients commonly have erythema of the posterior oropharynx and may have cervical adenopathy. (4) Historically, bullous myringitis was associated with *M pneumoniae;* however, studies evaluating the etiology of acute otitis media have rarely found *M pneumoniae* to be the cause; rather, it is caused by the typical causative agents of acute otitis media. (7) Auscultation of the lungs may reveal clear breath sounds early on in the illness; later on, crackles (rales) or wheezes may be detected. (5) Crackles are most likely to indicate *M pneumoniae* infection. (6) Increased work of breathing is typically absent. (1)

Asthma

M pneumoniae is thought to play a role in the pathogenesis of asthma exacerbations. Mouse models have shown that infection with *M pneumoniae* leads to bronchial constriction and increased resistance to airflow. (8) One study found that in patients with asthma, *Mycoplasma* may worsen symptoms and trigger an asthma exacerbation. In these children, *M pneumoniae* was detected in 20% of children hospitalized with an asthma exacerbation. In children who presented with new-onset wheezing, *M pneumoniae* infection was found in half of the patients, suggesting that *Mycoplasma* infection can trigger onset of asthma in those who are predisposed to developing the diagnosis of asthma. Treatment of infection in children with asthma is thought to be particularly important. (9)

Extrapulmonary Manifestations

A mucocutaneous rash is present in 10% of children with *M pneumoniae* and is fairly nonspecific. Several other skin manifestations have been associated with *M pneumoniae* infection, including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and the new clinical entity *M pneumoniae*–induced rash and mucositis (MIRM) (Fig 1). (10)(11)(12) EM and SJS are thought to be immune-mediated processes and have multiple inciting etiologies. Several outbreaks of SJS associated with *M pneumoniae* infection have also been reported. (11) MIRM is characterized by more than 2 sites of mucosal involvement; cutaneous involvement itself may or may not be present, distinguishing it from EM and SJS. If cutaneous manifestations are seen, lesions are typically targetoid or vesiculobullous. Patients with MIRM have a more benign disease

course than that of EM or SJS and typically make a full recovery, with recurrence in less than 10% of patients. (12)

M pneumoniae infection can cause anemia due to hemolysis from IgM autoantibodies that bind to the I-antigen on red blood cell membranes. These antibodies produce a cold agglutinin response during infection, triggering a hemolytic anemia. Patients with underlying hematologic diagnoses such as sickle cell anemia are particularly at risk. (13) Central nervous system manifestations can occur in up to 7% of patients hospitalized with *M pneumoniae* infections. A wide spectrum of central nervous system disease, including encephalitis, transverse myelitis, and cerebellar ataxia, have been reported. (14) Cardiac manifestations of *M pneumoniae* are rare, occurring in less than 10%, but cases of myocarditis, pericarditis, complete heart block, and hemopericardium have all been reported. (13)

DIAGNOSIS AND TREATMENT

Diagnostic Tests

Radiologic manifestations in *M pneumoniae* pneumonia are nonspecific and variable (Fig 2). The most common findings on chest radiography are peribronchial and perivascular interstitial infiltrates, which in one study were seen in 49% of patients. Airspace consolidations may also be seen, as well as bilateral peribronchial infiltrates. Unilobar disease may also be present, as well as pleural effusion. (15) For children with mild to moderate community-acquired pneumonia (CAP) in the outpatient setting, a chest radiograph is not recommended for diagnosis. (16)

Diagnosis of *M pneumoniae* can be challenging, and laboratory testing should be considered only if it will affect clinical decision making. Culture is not helpful as the organism is fastidious and growth can take 7 to 21 days. (1) Testing for *Mycoplasma* is rapidly evolving, with various diagnostic modalities discussed later herein. It is important to consider local availability of testing options and how quickly results will be available. Depending on the study, PCR and IgM serology are variably sensitive and specific in diagnosing acute infection, but sensitivity and specificity vary based on the specific assay that is used. (13)(17)(18)(19) Results of studies examining sensitivity and specificity are also variable depending on when testing is performed in the course of infection. (3)(17)(18)(19) Making an accurate diagnosis ideally entails obtaining real-time PCR combined with IgM serology, (13) but this is not always practical in the outpatient setting.

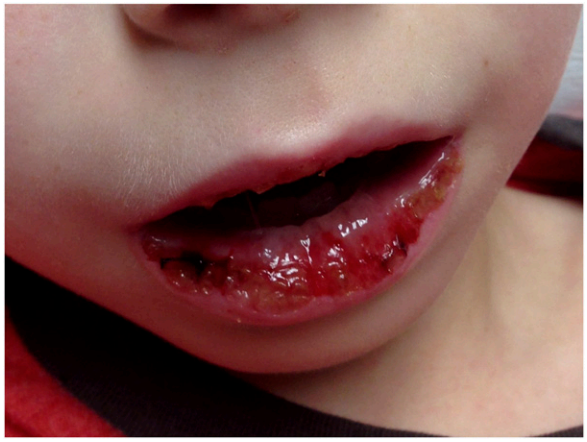

Figure 1. *Mycoplasma pneumoniae*–induced rash and mucositis on the lips. Note the hemorrhagic crusting. (Reprinted with permission from Jason Hawkes, MD, and VisualDx [http://www.visualdx.com]).

Commercially available, Food and Drug Administration (FDA)–approved, multiplex PCR assays using nasopharyngeal swabs are particularly sensitive in diagnosing *Mycoplasma* infections early on in infection, with sensitivity ranging from 80% to 100%. (2) However, proper collection of the nasopharyngeal sample is critical to obtain accurate results. PCR assays are useful in hospitalized patients with pneumonia, but given the expense associated with testing at this time, these assays are not used in the outpatient setting. PCR results remain positive for a median of 7 weeks after infection and, again, antibiotic drug therapy does not shorten the duration of positivity. (19)

M pneumoniae serologic tests, particularly enzyme immunoassays, are still commonly used to detect infection despite being less sensitive than PCR-based tests and despite no clear recommendations for their use. IgM antibodies to proteins and glycolipids are produced in response to infection and will rise within 6 to 10 days after infection. These antibodies peak after 3 to 6 weeks and then gradually decline but may be positive for months. (1) IgM antibodies are less specific in children younger than 19 years, and young children may not mount an immune response at all. A fourfold rise in IgG titers drawn 4 weeks apart is definitive for diagnosis and is often used as the gold standard. An accurate diagnosis is best made retrospectively by this method. (1)(17) Combination IgM-IgG assays have better specificities but lower sensitivities than IgM assays alone. (18) The 2011 Infectious Diseases Society of America CAP guidelines recommend specific testing before treatment for *M pneumoniae* in children (16) and definitely for a hospitalized patient.

There is no clear-cut recommendation for best practices regarding diagnostic testing. The decision to test should be made based on local testing availability and whether the results of testing will lead to a change in management.

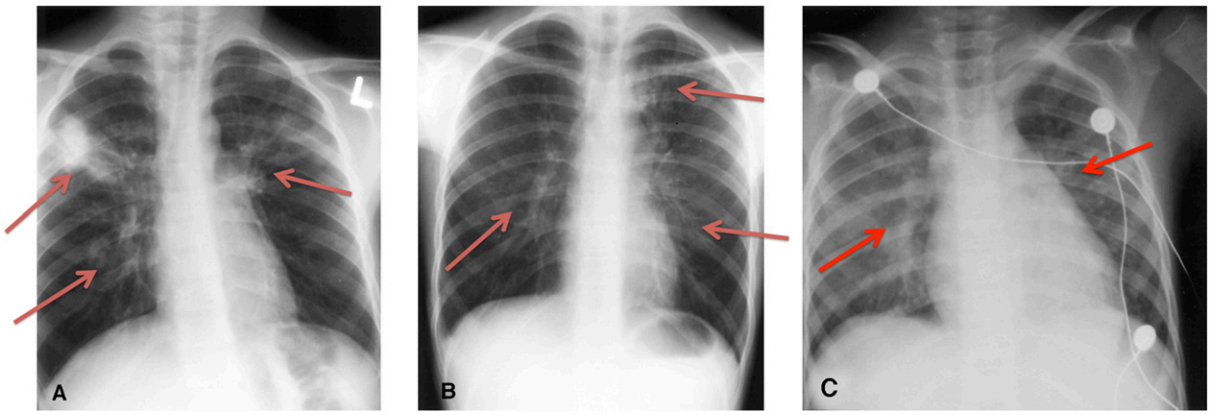

Figure 2. Radiologic features of *Mycoplasma pneumoniae* pneumonia. A. Bilateral pneumonia with major foci in the right upper, middle, and left upper lobes. B. Bilateral reticular pattern with accentuated left upper lobe involvement. C. Bilateral diffuse pneumonia with accentuation in the right lobes. (Reprinted with permission from Cimolai N. *Mycoplasma pneumoniae* respiratory infection. *Pediatr Rev.* 1998;19(10):327–332. Copyright © 1998 by the AAP.)

Management

Treatment of *M pneumoniae* is challenging because making an accurate diagnosis can be difficult, especially in the outpatient setting. Treatment could be considered in the school-age child and adolescent in whom CAP is suspected. Should the physician elect to treat, the recommended treatment is a macrolide antibiotic, ideally azithromycin, which is dosed 10 mg/kg on day 1, with a maximum of 500 mg, followed by 5 mg/kg on days 2 to 5, with a maximum dose of 250 mg. It is unclear whether the utility of azithromycin in treating children with *Mycoplasma* is due to its antimicrobial effects or its anti-inflammatory effects. (1)

Alternative regimens include erythromycin 30 to 40 mg/kg per day divided 4 times daily, with a maximum dose of 2 g, for 10 days; doxycycline 2 to 4 mg/kg either once or twice daily, with a maximum dose of 200 mg, for 10 days; or levofloxacin 10 mg/kg per dose daily, with a maximum dose of 500 mg, for 10 days. (16) Previously, doxycycline had been avoided in children younger than 8 years due to concern for staining of dental enamel; however, more recent data in younger children suggest that this is unlikely to be problematic. (20) Fluoroquinolones, however, should not be used in children younger than 18 years unless no alternative agents are suitable. (21)

In patients hospitalized with CAP due to *M pneumoniae*, treatment is recommended only if confirmatory testing for the organism has been performed. A systematic review performed in 2014 of pediatric patients showed limited value in treatment; most studies in the review found no benefit. If anything, treatment may be associated with 1 day less of fever. (22) There is no evidence that treating upper respiratory tract disease caused by *Mycoplasma* is useful, or for patients with extrapulmonary manifestations. (2) Patients with lower respiratory tract infection may benefit from antibiotic therapy, but there is no evidence that treating nonhospitalized children is useful. (2) Clearly, with better diagnostic tests, further research on the utility of treating children with *Mycoplasma* infections is warranted.

Due to their lack of a cell wall, *M pneumoniae* are inherently resistant to β-lactam antibiotics, requiring treatment with a macrolide or a tetracycline. *M pneumoniae* is generally susceptible to macrolides, but macrolide resistance is developing, with the highest prevalence of resistant strains seen in children. Resistance also has a geographic predilection, with higher rates seen in Asia than in Europe and North America. Among hospitalized children with a macrolide-resistant strain, infections were generally more severe than those with susceptible strains. (13) Alternatives to macrolides include tetracyclines and fluoroquinolones, as discussed previously herein. (16)

Criteria for hospitalization in children with pneumonia include hypoxia (oxygen saturation <90%), tachypnea, signs of respiratory distress (grunting, nasal flaring), and dehydration. In addition, children with underlying comorbidities that predispose them to more serious illness may require hospitalization. (23) Fortunately children with *Mycoplasma* do not often require hospitalization. Figure 3 shows the suggested management of pneumonia.

CLINICAL CASE: MANAGEMENT

The patient in the opening clinical case vignette has been ill for approximately 2 weeks and now has persistent cough and bilateral crackles present on lung examination. Diagnostic testing was deferred. She was started on a

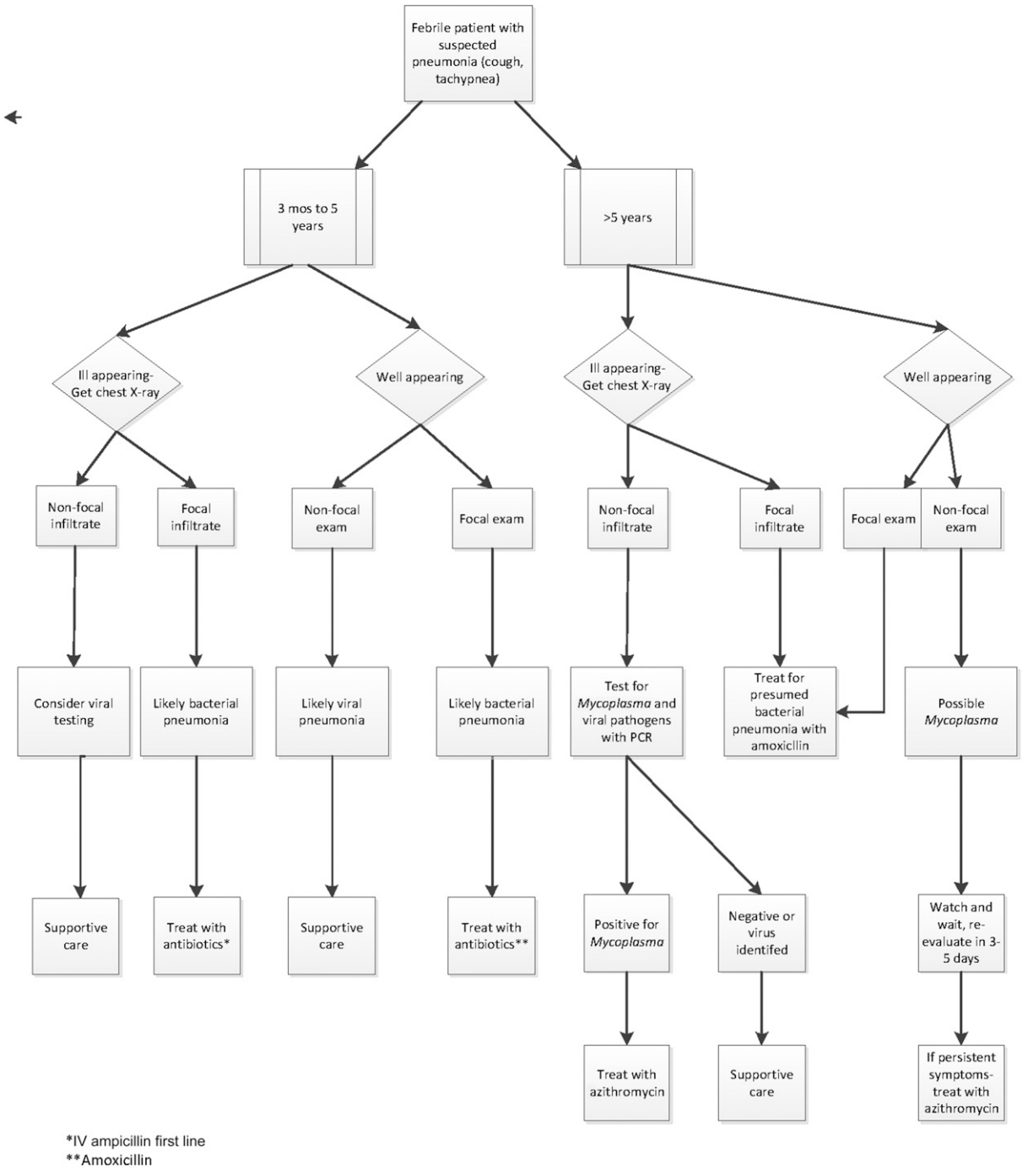

Figure 3. Decision tree for the treatment of children with suspected pneumonia.

5-day course of azithromycin given her persistent fevers and examination consistent with atypical pneumonia.

CONCLUSION

M pneumoniae is a common cause of CAP in children and adolescents. Clinical findings may be suggestive of *M pneumoniae* pneumonia, yet diagnosis is challenging because neither clinical nor radiographic features are specific for this infection. An accurate diagnosis is best conducted with real-time PCR combined with IgM serology, (13) but this is most feasible in an inpatient setting. Development of a rapid, point of care test that is reliable, inexpensive, and readily available could help guide clinical decision

making. Further research is needed regarding the utility of treatment in the otherwise healthy child with CAP in the outpatient setting.

Summary

- *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia in children and adolescents and needs to be recognized by physicians. Findings associated with *M pneumoniae* infection are nonspecific and difficult to distinguish from other causes of respiratory tract infections. Chest radiography is nonspecific and findings are variable. (4)(5)(6)(7)
- No firm recommendation exists at this time, but testing for children with suspected *M pneumoniae* pneumonia should be reserved for those who are hospitalized or in whom testing will alter management. (2)(16)
- Based on evidence, choice of test depends on the location of the patient (inpatient versus outpatient), availability, and cost. The currently recommended method of diagnosis is by polymerase chain reaction testing, but based on cost and availability, this should be reserved for inpatients. (2)(16)
- Treatment of *M pneumoniae* is best accomplished with azithromycin in children whose clinical picture is consistent with atypical pneumonia, but other regimens are available. (16)

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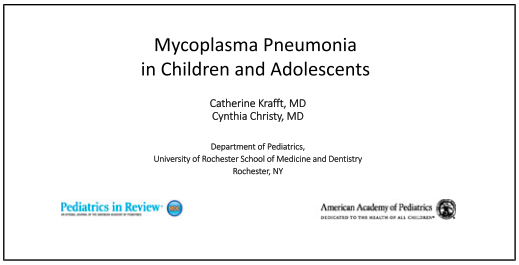

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1. A previously healthy 9-year-old girl is seen in the emergency department in January with a 5-day history of worsening cough, malaise, and low-grade fever. Before the cough she had a sore throat and rhinorrhea for 6 days. Her 10-month-old brother was hospitalized with bronchiolitis 5 weeks ago. Several classmates at school have had "cold" symptoms over the past month. The family dog was diagnosed as having "kennel cough" last week. The family lives on a ranch in Arizona. On physical examination the patient has an erythematous posterior pharynx, and bilateral crackles are heard on lung examination. The remainder of her examination findings are normal. Which of the following best describes the mechanism by which she most likely acquired her infection?
    A. *Histoplasma capsulatum* airborne spores.
    B. *Bordetella bronchiseptica* airborne particles from her dog.
    C. *Mycoplasma pneumoniae* droplet contact from a classmate.
    D. Nasal secretion direct contact containing *M pneumoniae* from her dog.
    E. Nasal secretion direct contact containing parainfluenza virus from her brother.
2. A previously healthy 5-year-old boy is seen in the office for a 1-day history of right-sided earache. He has had nasal congestion, headache, and a mild intermittent cough for 2 to 3 days. On physical examination, his temperature is 100.8°F (38.2°C). His left tympanic membrane is normal. There are 2 bullae noted on the right tympanic membrane. His posterior pharynx is normal and his lungs are clear to auscultation. Infection from which of the following is the most likely etiology of his otalgia?
    A. Enterovirus.
    B. *Haemophilus influenza* type B.
    C. *M pneumoniae.*
    D. *Staphylococcus aureus.*
    E. *Streptococcus pneumoniae.*
3. A previously healthy 13-year-old boy is seen in the office with a 2-day history of painful sores on his lips, in his mouth, and on his penis. He is not drinking due to the pain and is also having difficulty urinating. He also complains of his eyes hurting, and his mother states that the white part of his eyes has been very red. He had onset of cough and fever 8 days ago. Two siblings have also had cough and fever. Physical examination is remarkable for injected conjunctivae bilaterally with a watery discharge, numerous vesico-ulcerative lesions of his oral mucosa and lips, and vesicobullous lesions of his penis to include involvement of his urethra. He does not have any rash. Which of the following is the most likely diagnosis?
    A. Erythema multiforme.
    B. Erythema urticaria.
    C. Kawasaki disease.
    D. *M pneumoniae*–induced rash and mucositis.
    E. Stevens-Johnson syndrome.

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4. A previously healthy 11-year-old girl is admitted to the hospital from the emergency department (ED) with a 6-day history of increasing nonproductive cough, malaise, and intermittent fever. Before the onset of her cough she had nasal congestion, headache, and a sore throat. Her 14-year-old sister was diagnosed as having *M pneumoniae* infection 2 weeks ago. Pulse oximetry in the ED showed an oxygen saturation on room air of 88%, with a respiratory rate of 32 breaths/min. Her oxygen saturation increased to 96% with supplemental oxygen by nasal prongs. Lung auscultation reveals bilateral crackles. A chest radiograph shows bilateral peribronchial and perivascular interstitial infiltrates. Which of the following is the most appropriate next step in diagnosis?
    A. Arterial blood gas.
    B. Computed tomography of the chest.
    C. *Mycoplasma hominis, M pneumoniae,* and *Chlamydia trachomatis* serum IgG assays.
    D. *Mycoplasma pneumoniae* serum IgM and nasopharyngeal polymerase chain reaction.
    E. Routine throat culture.
5. A 12-year-old boy with moderate persistent asthma is admitted to the hospital from the ED for an acute asthma exacerbation. He was afebrile in the ED. A nasopharyngeal swab was obtained and a multiplex polymerase chain reaction panel for respiratory pathogens was positive only for *M pneumoniae.* A chest radiograph shows bilateral peribronchial interstitial infiltrates and no focal infiltrates. In addition to management for his asthma, which of the following is the most appropriate therapy?
    A. Intravenous cefazolin.
    B. Intravenous levofloxacin.
    C. Intravenous vancomyin.
    D. Oral azithromycin.
    E. Oral levofloxacin.

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