Cold Weather Viruses

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Education Gap

Clinicians must learn to identify viral infections in children during the winter months and must practice caution with the use of unnecessary medications in such cases. Recognition of the clinical pattern of viral infection (eg, bronchiolitis) in conjunction with judicious use of viral tests (either office-based immunoassays or newer molecular tests) may assist in epidemiological monitoring, cohorting patients in the hospital, withholding unnecessary therapies, and providing a definitive diagnosis.

Objectives

After completing this article, readers should be able to:

1. Review the epidemiological aspects and clinical signs and symptoms of common cold weather viruses.
2. Recognize situations in which viral testing is indicated.
3. Recognize situations in which treatment is indicated.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
Adv	adenovirus
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
hMPV	human metapneumovirus
PCR	polymerase chain reaction
PIV	parainfluenza virus
RSV	respiratory syncytial virus
RV	rhinovirus

CASE

In early November you are evaluating a 9-month-old boy born at 33 weeks of gestation. The infant presents with 2 days of fevers (101°F–102°F [38.3°C–38.8°C]), copious rhinorrhea, and 1 day of coughing with difficulty breathing. He is otherwise feeding well and has had adequate urination. His 4-year-older sister has an upper respiratory tract infection.

On physical examination, the infant has a respiratory rate of 45 breaths/min without chest wall retractions. On auscultation there is good air entry with scattered rhonchi bilaterally. What is the most appropriate next step in management?

a. Obtain respiratory syncytial virus (RSV) and influenza antigen testing.
b. Obtain a chest radiograph to look for focal infiltrate.
c. Provide supportive care with nasal suctioning, fever control, and attention to adequate fluid intake.
d. Perform a trial of nebulized albuterol in the office.

This case represents a common scenario encountered by pediatricians during the winter months in the United States. The winter season in the Northern hemisphere begins in late December and ends in late March. An increase in the number of viruses causing infections begins 1 to 2 months before and continues

for several weeks to months after the winter season. The reasons why cold weather is associated with a rise in viral infections is likely due a longer time spent indoors, the ability of certain viruses such as influenza to survive in cold temperatures, and low humidity. (1)

The infant in the previously described case has clinical bronchiolitis. The latest clinical practice guidelines (2) from the American Academy of Pediatrics (AAP) from 2014 recommend supportive care in patients with viral bronchiolitis [correct answer: c]. RSV is the most common cause and is responsible for 80% of bronchiolitis-associated hospitalizations in children. (3) Other cold weather viruses, such as influenza, parainfluenza virus (PIV) type 3, human metapneumovirus (hMPV), adenovirus (Adv), and rhinovirus (RV), also cause bronchiolitis illness. It is hard to distinguish RSV bronchiolitis from other causes of viral bronchiolitis based solely on history or physical examination findings.

The clinical practice guidelines do not recommend routine testing for viral bronchiolitis because it does not change management for the individual patient. However, the advent of newer multiplex polymerase chain reaction (PCR) assays can assist with a definitive diagnosis. Specific diagnosis can help in cohorting hospitalized children and provides objective data to limit the use of unnecessary medications. Chest radiographs are not routinely recommended because the presence of infiltrates does not correlate with disease severity or bacterial superinfection.

In this article we provide a review of common respiratory viral infections seen in the cold weather months. RSV and influenza account for most of these infections during the winter months and cause annual outbreaks from late fall to early spring. This review also includes other important viruses responsible for respiratory infection in children, ie, PIV (peak in fall and spring), hMPV (peak in late winter and fall but activity is seen throughout the year), respiratory Adv (throughout the year), and RVs (year-round, with increased prevalence from September through May) (Fig).

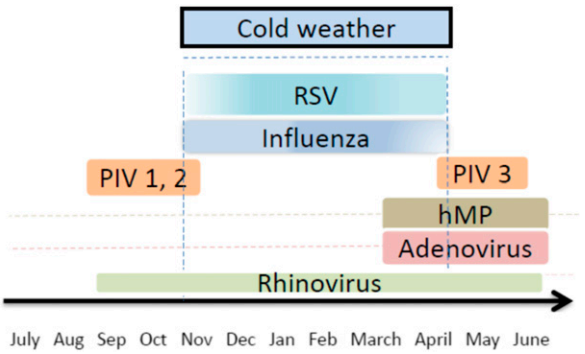

Figure. Duration of activity of common cold weather viruses. Respiratory syncytial virus (RSV) and influenza activity are seen only in the winter months; parainfluenza virus (PIV) types 1 and 2 are seen in fall and PIV-3 in spring; human metapneumovirus (hMPV) infections are seen throughout the year but peak in later winter and spring; and adenovirus is seen throughout the year, but epidemic respiratory adenovirus may occur in later winter and spring.

RESPIRATORY SYNCYTIAL VIRUS

Introduction

RSV is the most common cause of annual winter outbreaks of lower respiratory tract disease in infants and young children. Worldwide RSV is responsible for an estimated 3.4 million hospitalizations annually in children younger than 5 years. (4) Every year in the United States on average approximately 57,000 RSV-associated hospitalizations occur in children younger than 5 years, and the annual costs are approximately $2.6 billion. (5)(6) Prematurity in infants, underlying chronic lung disease, and heart disease are risk factors for severe RSV infection in children; however, the largest number of RSV hospitalizations occur in healthy infants. The estimated RSV pneumonia-related mortality in the United States is 3.1 per 100,000 person-years in children younger than 1 year. (7)

Epidemiological Profile. RSV infection is primarily seen in the winter months throughout the United States except in Florida, where it extends throughout much of the year. Nationally, onset of the RSV season ranges from mid-September to mid-November, peaks from mid-December to mid-February, and the season offset occurs mid-April to mid-May. In tropical climates, peak RSV activity correlates with the rainy season. (8) RSV circulation also seems to differ for Hawaii based on limited data. An insufficient number of laboratories in Hawaii report RSV antigen and RSV PCR results to the National Respiratory and Enteric Virus Surveillance System, but RSV activity seems to be present throughout the year. In Texas, RSV activity begins typically in September or October and peaks in December or January.

Transmission. RSV is transmitted primarily via inoculation of nasopharyngeal mucosa or conjunctiva through direct contact with viral-containing secretions, fomites, or droplets. RSV can survive 4 hours on hands and fomites.

RSV spreads effectively through exposed family members. In a prospective study of families with an infant and older siblings, 44% of the families became infected with RSV within 3 months, and in almost all cases an older sibling (2–16 years old) introduced the virus into the family. (9) The incubation period is 2 to 8 days (Table).

Clinical Features

Primary Infection. Almost all children are infected with RSV at least once by 2 years of age. The primary infection in an

TABLE. Characteristics of Common Cold Weather Viruses

CHARACTERISTIC	RSV	INFLUENZA	HMPV	PIV	ADENOVIRUS	RHINOVIRUS
Seasonality	Begins early winter, peaks January or February, ends early spring	Begins late December and January (predominant strain A), ends early spring (predominant strain B)	Present throughout the year, peaks late winter and early spring	PIV-1 and -2 are seen in fall, PIV-3 in spring and early summer	Activity is present throughout the year, strains 3 and 7 cause respiratory disease	Year-round, with peak in winter months, September–May
Incubation period, d	2–8	2–3	5–9	2–4	5–7	2–3
Common clinical features	Fever Rhinorrhea Congestion Bronchiolitis Viral pneumonia	Fever Pharyngitis Cough Gastrointestinal symptoms Malaise Myalgias	Fever Rhinorrhea Congestion Bronchiolitis Viral pneumonia	PIV-1 and -2: croup PIV-3: bronchiolitis, viral pneumonia	Fever (prolonged) Pharyngitis Conjunctivitis Laryngotracheitis Pneumonia Pneumonia, hepatitis, cystitis, colitis in immunocompromised patients	Common cold with nasal discharge and cough Increased severity and duration of asthma
Preferred method of testing	PCR assay Sn 100% Sp 89% Other Rapid antigen Cell culture	PCR assay Sn 86%–100% Sp 89% Other Rapid antigen Sn 54%, Sp 100%	PCR assay Sn 94% Sp 99%	PCR assay Sn 95%–100% Sp 95%–100%	PCR assay Sn 83%–90% Sp 98% Other Serology Cell culture	PCR Sn 90%–100% Sp ~95% Reported separate or with enterovirus Rhinovirus + PCR in infants likely represents infection within 30 d
Treatment	Supportive	Supportive or oseltamivir	Supportive	Supportive (dexamethasone for croup)	Supportive (cidofovir in immunocompromised patients)	Supportive
Prevention	Hand hygiene Palivizumab in high-risk patients	Hand hygiene, annual vaccination Antiviral drug prophylaxis	Hand hygiene	Hand hygiene	Hand hygiene	Hand hygiene Investigational: interferon-γ, pleconaril

hMPV=human metapneumovirus, PCR=polymerase chain reaction; PIV=parainfluenza virus, RSV=respiratory syncytial virus, Sn=sensitivity, Sp=specificity.
Data from the work of Joseph Greensher, MD (unpublished data).

infant is almost always symptomatic, ranging from mild upper respiratory tract symptoms to severe bronchiolitis. A 2- to 4-day illness with low-grade fevers, rhinorrhea, and nasal congestion (upper respiratory tract symptoms) is followed by cough, tachypnea, and increased respiratory effort manifested by subcostal, intercostal, supraclavicular retractions; nasal flaring; and grunting (lower respiratory tract symptoms). (10) Bronchiolitis is more commonly the manifestation of primary RSV infection in infants as opposed to young children 2 to 5 years of age. Lower respiratory tract disease occurs more frequently in children with underlying cardiopulmonary disease, those in closed populations such as group child care centers, and children of American Indian and Alaskan native background. Viral pneumonia in RSV infection can coexist with bronchiolitis without evidence of secondary bacterial infection.

Course of Illness. The course of bronchiolitis varies and may require serial observations to adequately assess illness acuity. The decision to hospitalize an infant with RSV infection can be challenging. Among the more consistent and reliable findings in severe RSV disease are decreased oxygen saturations; therefore, hypoxia (oxygen saturation ≤90%) in an infant should be considered an indication for further inpatient monitoring. Rapid fluctuations in clinical manifestations are characteristic of RSV; therefore, serial assessments in either the office or the hospital are helpful.

Typical Findings on Examination and Chest Radiography. The auscultatory findings of bilateral crackles and scattered wheezing may be present on the initial examination and absent thereafter; this variability in physical examination findings within hours is characteristic of RSV infection. The chest radiography findings in RSV infection include hyperinflation with hyperlucency of the lungs, flattened diaphragm, and peribronchial thickening. Patchy areas of atelectasis may be present, more frequently in the right middle and upper lobes. Areas of atelectasis may be large and misinterpreted as consolidation. The current AAP guidelines do not recommend a routine chest radiograph because bronchiolitis is diagnosed based on clinical and physical clues and the radiography findings do not aid in management decisions. In fact, the finding of an infiltrate may increase the risk of inappropriate antibiotic drug use. Bacterial pneumonia in infants with bronchiolitis without consolidation is unusual. Antibiotic drug therapy may be justified in rare cases of bronchiolitis in which intubation and mechanical ventilation for respiratory failure are required.

Complications. Apnea may be present at the onset of illness in 1% to 20% of hospitalized infants. Most of the infants do not have apnea later in the course of infection or with subsequent infections. Apnea is more frequent in premature infants, at young chronological age (≤1–2 months), and in infants with a history of apnea of prematurity.

Coinfection with bacterial pathogens is rare in RSV infection and was found in 1.2% of children infected with RSV in 1 study. (11) Urinary tract infection is the most frequent secondary bacterial infection. Respiratory disease from bacterial coinfection with *Streptococcus pneumoniae* or *Staphylococcus aureus* is uncommon. Codetection of RSV with other viral pathogens is seen in approximately one-third of the cases using multiplex PCR assay; however, the significance of this finding on morbidity and length of stay is not clear. (12)

Diagnosis

A presumptive diagnosis of RSV infection is made based on either upper respiratory tract symptoms or bronchiolitis in infants and young children in the winter months. Routine testing of outpatients and hospitalized patients with bronchiolitis is not recommended in the clinical practice guidelines.

When to Test? Clinically it is not possible to distinguish between different viruses as the cause of bronchiolitis. Therefore, viral testing is useful for epidemiological monitoring, cohorting patients in the hospital, and providing a definitive diagnosis. In this era of antimicrobial stewardship, use of viral testing has shown mixed results in limiting antibiotic drug use. In our institution, stewardship efforts to reduce antibiotic drug use in confirmed RSV infection were possible with the availability of these objective data. (13)

What Tests to Use? During the past 5 to 10 years, the availability of multiplex PCR has proved to be the most sensitive method of viral detection. Other methods for RSV detection, although less commonly available, include standard culture or shell viral assay as well as immunoassays. Antigen detection assays for RSV are less sensitive than PCR but have good specificity and are less expensive.

There are 6 commercially available multiplex PCR assays (nested PCR), with sensitivity and specificity of 100% and 89%, respectively, with some variability in performance. (14) The average duration of RSV detected by PCR is approximately 11 days, but it can be up to 4 weeks in young infants and immunocompromised older children. Given the increased sensitivity of PCR, it can detect low-level asymptomatic shedding in the convalescent phase from a previous RSV infection, although prolonged asymptomatic shedding is not as common as seen with other viruses, such as RV. (15)

A dipstick immunoassay from a nasopharyngeal specimen allows the capture and visual detection of RSV fusion protein, which can be used as a rapid test in the office setting. It can provide results in 15 minutes and has pooled sensitivity and specificity of 81% and 97%, respectively, in children. (16)

Serological testing is reserved for epidemiological research purposes because it is generally not helpful in the diagnosis of acute RSV infection. In the past, viral culture was the standard, but it takes 3 to 5 days to observe a syncytial cytopathic effect, in addition to the expertise required.

Treatment

The mainstay of treatment in infants and young children with RSV infection is supportive care, mainly attention to hydration and respiratory support. The use of bronchodilators, corticosteroids, or inhaled hypertonic saline is not recommended by the clinical practice guidelines because no benefit has been confirmed with these treatment modalities.

When to Use Ribavirin? Ribavirin is a nucleoside analogue that is Food and Drug Administration (FDA) approved for the treatment of RSV via small particle aerosol. However, it is not recommended because of unproven efficacy, expense, and potential untoward adverse effects from environmental exposure. Its use in RSV infection is limited to severely immunocompromised hosts with severe RSV infection, and even in these patients the question of benefit remains.

Prevention

Prophylaxis. Immunoprophylaxis against RSV is attainable with palivizumab. It is the only product available to reduce the risk of RSV infection. It is a humanized monoclonal antibody that targets a highly conserved epitope on the RSV F glycoprotein. Two randomized, multicenter, double-blind, placebo-controlled trials have shown a reduction in RSV-related hospitalization by 50% to 55%. (17)(18) It was approved by the FDA in 1998.

The current AAP guidelines recommend prophylaxis with palivizumab in:

1. Otherwise healthy infants who were born at less than 29 weeks 0 days of gestation plus 12 months or younger at the start of the RSV season. (19)
2. Infants in their first year after birth who have chronic lung disease using the definition of a requirement for supplemental oxygen through the first 28 days of life and again in their second year of life if they continue to require medical therapy (largely oxygen) for chronic lung disease within 6 months of the onset of the RSV season.
3. Infants younger than 12 months with acyanotic or cyanotic heart disease who are receiving medication to control heart failure and will require cardiac surgery.

Palivizumab is administered intramuscularly at a dose of 15 mg/kg once every 30 days throughout the RSV season up to 5 doses. Currently, studies of monoclonal preparations with longer half-life and increased affinity for the virus are underway and, if successful, could allow prophylaxis with a single dose.

Improved understanding of the structure of RSV and the importance of the prefusion protein has led to a tremendous increase in RSV vaccine development during the past decade. Approximately 60 vaccine candidates are in different stages of development. This vaccine pipeline is diverse and promising, and a safe and effective vaccine may well be available in the next 5 to 10 years.

Another important aspect of prevention of RSV infection in high-risk infants is education of caregivers on hand hygiene, avoidance of crowded places, and reduction of secondhand smoke exposure. Palivizumab does not have a role in treatment of RSV infection or in preventing nosocomial transmission of infection.

INFLUENZA VIRUS

Introduction

Influenza infection typically occurs during the late fall through early spring in the United States, peaking typically in February in most of the country. (20) Influenza is a significant cause of morbidity and mortality in children. (20)(21) Symptoms of uncomplicated infection typically include fever, chills, headache, malaise, myalgia, and nonproductive cough. Nasal congestion, sore throat, otitis media, and myositis may also occur. Nausea, vomiting, and diarrhea are more common in children than in adults. (22) However, young children (<5 years of age) commonly present only with signs of a febrile upper respiratory tract infection, whereas older children (≥5 years of age) may additionally report headache, malaise, and myalgia. In infants, influenza can cause various lower respiratory tract infections, including croup, bronchiolitis, and/or pneumonia. (23)

Prompt identification of high-risk persons with influenza infection is crucial because they are at increased risk for complications. High-risk persons include children younger than 5 years (and especially <2 years, who have higher rates of hospitalization for complications), those with chronic disease (including, but not limited to, asthma, sickle cell disease, diabetes mellitus, cerebral palsy, seizure disorders, and moderate to severe developmental delay), immune compromise, and morbid obesity (BMI ≥40). (20) Complications of influenza may include secondary bacterial infections (most commonly *S aureus*, group A *Streptococcus*, and *S pneumoniae*), myocarditis, encephalitis, respiratory failure, shock, and/or a sepsislike illness. (23)

Diagnosis

The Centers for Disease Control and Prevention (CDC) advocates clinically diagnosing influenza infection based on signs and symptoms in the appropriate epidemiological

setting. (24) An influenzalike illness is defined as fever (temperature ≥100°F [≥37.8°C]), cough, and/or sore throat in the absence of another known cause. (23) Confirmation by diagnostic testing is not required, and neither should it delay initiation of antiviral medication. (25) However, clinical diagnosis of influenza in pediatrics is somewhat restricted because there are many shared signs and symptoms with other respiratory pathogens. Younger children (<6 years of age) have particularly greater overlap. (20) Furthermore, the epidemiology of coinfections with influenza remains difficult to assess secondary to lack of outpatient diagnostic information. (22)

These challenges can ideally be overcome with diagnostic testing, which can provide important clarifications about etiology. Specimens for diagnostic testing should ideally be collected within the first 72 hours of illness because the quantity of viral particles shed decreases as illness progresses. (23) Molecular assays, especially reverse transcriptase PCR tests, are highly accurate and considered the gold standard of testing. These assays can detect nucleic acids in respiratory specimens for extended periods and have improved sensitivity compared with rapid antigen detection assays. (26) Although less expensive and more available, clinicians must consider the heightened potential for false-negative results when using rapid antigen modalities during the peak of influenza season. The positive predictive value of rapid antigen tests will be lower during periods of low influenza activity. (27)

Treatment

Severity of disease, duration of symptoms, and presence of underlying conditions are important considerations when deciding to administer antiviral drug therapy. Antiviral drugs for influenza are most beneficial when started as close to illness onset as possible. The Infectious Diseases Society of America recommends prompt treatment (ideally, <48 hours from the start of symptoms) for patients in high-risk groups or those who are severely ill for 1 to 5 days. (24) Recently, Malosh et al (28) reported the findings from a meta-analysis of 5 randomized controlled trials of early oseltamivir treatment. Oseltamivir treatment started within 24 hours of onset reduced illness duration significantly more than when started 24 to 48 hours after onset (22.8 versus 4.4 hours). Oseltamivir, a neuraminidase inhibitor, acts as a competitive inhibitor by binding in the enzyme's active site. The primary function of the neuraminidase enzyme in the life cycle of influenza viruses is to remove sialic acid residues from the surface of the infected cell and from mucins in the respiratory tract, facilitating the release of newly synthesized virus particles and allowing the virus to spread. Early blockade of this activity by neuraminidase inhibitors prevents virion budding and leads to aggregation of viruses on the cell surface, preventing subsequent infection of new cells.

Any person requiring hospitalization for influenza should be treated empirically because they are at greater risk for complications. In hospitalized patients, treatment with oseltamivir up to 96 hours after illness onset has been shown to reduce severe clinical outcomes. In patients with prolonged illnesses, clinical judgment should guide the need to extend treatment beyond 5 days. (29) In the outpatient setting, patients who are not at high risk should be considered for treatment only if presenting within 48 hours of illness onset because it may also provide some benefit (eg, a shorter duration of illness). (24)(25)

There are 3 antiviral medications currently available to treat influenza in children: oral oseltamivir (treatment in infants 1–8 months old: 3 mg/kg per dose twice daily; 9–11 months old: 3.5 mg/kg per dose twice daily; children 12–23 months old: weight ≤15 kg: 30 mg twice daily for 5 days, weight >15–23 kg: 45 mg twice daily for 5 days; and children ≥2–12 years old and adolescents: weight ≤15 kg: 30 mg twice daily for 5 days, weight >15–23 kg: 45 mg twice daily for 5 days, weight >23–40 kg: 60 mg twice daily for 5 days, weight >40 kg: 75 mg twice daily for 5 days; prophylaxis is not recommended <3 months of age, >3 months the dose is same as treatment and the duration is 7 days), inhaled zanamivir (children ≥5 years old and adolescents: 2 inhalations [10 mg] once daily for 10 days), and, most recently, intravenous peramivir (children ≥2 years old: 12 mg/kg as a single dose; maximum dose: 600 mg per dose; adolescents: 600 mg as a single dose). All 3 of these medications inhibit viral neuraminidase activity and prevent viral release from host cells. To date, resistance has not been a clinically significant occurrence. (20)(22)(23) A new antiviral agent, baloxavir was approved in October 2018 for use in patients older than 12 years with uncomplicated influenza. It is a cap-dependent endonuclease inhibitor and requires single-dose administration. As per the AAP recommendations, oseltamivir is the drug of choice for the treatment of influenza in children and may be used in infants 14 days and older, although there is limited efficacy and safety data in children younger than 3 months. (29) The FDA approves treatment with oseltamivir for children as young as 2 weeks. (30) Peramivir is approved for acute influenza in children 2 years and older. Zanamivir, administered by disk inhaler, may be used as an alternative in children 7 years and older. Recommended treatment dosages vary by the weight of the child.

The most common adverse events experienced with oseltamivir and peramivir use include vomiting and nausea. Zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease. Less common

adverse events of zanamivir may include diarrhea, nausea, sinusitis, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections. (30)

Prevention

The best preventive measure against influenza is seasonal, yearly vaccination for children 6 months and older. (22) There are 2 forms of the vaccine: an inactivated form administered intramuscularly and a live-attenuated form administered intranasally. (23) In previous influenza seasons, the Advisory Committee on Immunization Practices recommended exclusive use of the inactivated influenza vaccine after data showed decreased effectiveness (especially for H1N1 influenza strains) with use of the intranasal formulation. Currently, there is new evidence to support the use of a reformulated live-attenuated formulation, and the Advisory Committee on Immunization Practices has voted to recommend both vaccines for protection for the 2018-2019 season. (21) However, the AAP strongly recommends preferential use of the inactivated vaccine. (31) Influenza vaccine effectiveness is moderate, and a history of influenza vaccination in the season does not exclude an influenza diagnosis. Individuals with egg allergies may safely receive the vaccine without any additional precautions.

Chemoprophylaxis with antiviral medication is not a substitute for influenza vaccination. When deciding whether to administer chemoprophylaxis, the exposed person's risk of complications and the type and duration of contact should be considered. Oseltamivir is FDA approved for chemoprophylaxis of influenza in children 3 months and older. Zanamivir is approved for chemoprophylaxis of influenza in children 5 years and older. Peramivir is not currently approved for preventive use in children. (24)(25)

To achieve maximum efficacy, antiviral drugs for preexposure chemoprophylaxis must be taken for the duration of influenza exposure. However, extended use of these drugs may select for resistance, and the adverse effects associated with prolonged use are unclear. Oseltamivir use for up to 42 days has been well tolerated, but there are no published data available for longer regimens. (32) Preexposure chemoprophylaxis should be reserved for persons at very high risk for complications.

Postexposure chemoprophylaxis is indicated within 48 hours for close contacts of a person with influenza and is typically given for 10 days after the reported exposure. Candidates include unvaccinated household members or other close contacts at higher risk for complications. Note that persons receiving chemoprophylaxis may still acquire influenza infection and be potentially able to transmit influenza virus. (23)(24)(25)

PARAINFLUENZA VIRUS

Among the PIVs, the most common type is PIV-3, acquired by two-thirds of infants by 12 months of age. (33) PIV-1 infections occur most commonly in the fall as the weather turns colder. PIV-2 disease has more sporadic seasonal activity, and PIV-3 is most prominent during spring and summer but may continue into the colder months of fall. (33)(34) The seasonality and clinical manifestations of PIV-4 infection are less well described. (35) Most PIV infections affect the tracheobronchial and lower respiratory tracts, but influenzalike illnesses have also been reported. PIV-1 is the major cause of croup (laryngotracheobronchitis), and, less commonly, PIV-2 has been isolated. (34)(35) PIV-3 is associated with pneumonia and bronchiolitis. (35) Seasonal PIV epidemics cause up to 75% of croup. (36) Reinfection with PIV is common because immunity is transient, but reinfections are typically milder and limited to the upper respiratory tract. As with other viruses, reverse transcriptase PCR assays are the most sensitive diagnostic method for detection of PIV. Currently, there is no vaccine available against PIV. Treatment is supportive because most PIV infections are self-limited. There are no specific therapies available for PIV, although several are in development. (33)(35) For example, an experimental antiviral, DAS181, is a sialidase fusion protein that cleaves the sialic acid–containing receptors of PIV in respiratory cells. It has been reported to successfully treat PIV in patients with hematopoietic cell and lung transplant when considered for compassionate use. For mild croup, dexamethasone given as a single oral dose has been shown to improve symptoms.

ADENOVIRUS

Although Adv infections occur year-round, epidemic respiratory disease may occur in the winter and early spring. (37)(38) Respiratory Adv infection has a broad spectrum of presentation, ranging from symptoms of "the common cold" to pneumonia. Adv may also cause pharyngitis/tonsillitis, keratoconjunctivitis, croup, bronchiolitis, otitis media, hepatitis, gastroenteritis, meningitis, or encephalitis. (39) The latter 2 infections are more common in young infants and the immunocompromised, 2 populations at high risk for developing severe disease secondary to lack of humoral immunity. (38)(40) PCR assays are the preferred diagnostic method; however, intermittent and persistent shedding after Adv infections

may pose a challenge in interpreting PCR results. (39) Furthermore, immunocompromised hosts may shed the virus for weeks or longer. (38) Studies have shown that detection of Adv DNA in peripheral blood is indicative of a high risk of disseminated disease. (41) Treatment is supportive. (39) There is a live, oral Adv vaccine, targeted for serotypes 4 and 7, approved by the FDA in 2011 for exclusive use in military personnel aged 17 to 50 years at higher risk for lower respiratory tract infection from these serotypes. (38) Several studies have shown limited treatment success using various antiviral drugs, including cidofovir and ribavirin. (37) Cidofovir use is generally reserved for immunocompromised patients with severe, life-threatening infections. In a study of neonatal Adv infections, ribavirin or cidofovir treatment did not improve outcomes. (42)

HUMAN METAPNEUMOVIRUS

hMPV is a paramyxovirus discovered in 2001 associated with respiratory tract disease in children. In temperate regions it is present throughout the year, with peaks in late winter and early spring. (43) The incubation period is 5 to 9 days. hMPV causes both upper and lower respiratory tract disease in children. Similar to RSV, the upper respiratory tract disease presents as rhinorrhea, cough, and fevers and the lower respiratory tract disease presents as bronchiolitis, croup, pneumonia, or asthma exacerbation. (44) In contrast to RSV, the rate of hMPV-related outpatient visits remains similar in older children compared with younger infants. Thus, hMPV causes clinically significant disease throughout early childhood similar to influenza. (43) In healthy children, viral shedding is usually 7 to 14 days, but in immunocompromised individuals it can be prolonged. (45) hMPV has been associated with neurologic manifestations, including febrile seizures, status epilepticus, and encephalopathy. (46) Molecular technology based on nucleic acid amplification assay can reliably diagnose hMPV infection. (47) The treatment is mainly supportive care. Ribavirin and oligoclonal immunoglobulins possess anti-hMPV in vitro activity, (48) but there is no proven benefit in management besides anecdotal reports in immunocompromised hosts. (49) There is no available vaccine or prophylactic antibody for prevention, but there are several candidates in development.

RHINOVIRUS

RVs are one of the most common causes of common cold and account for almost 50% of the upper respiratory tract infections in children and adults. (50)(51) RVs are members of the *Enterovirus* genus in the family *Picornaviridae*. Other members of the *Enterovirus* genus include polioviruses, Coxsackie viruses, and echoviruses. (52) RVs cause infections year-round, with seasonal peaks during the cold weather months, September through May. (53)

RV infections in any age group typically cause only mild upper respiratory tract illness. Children can have fever during the first 2 to 3 days and moderate enlargement of the anterior cervical lymph nodes. Illness generally lasts 5 to 7 days in adults, but it can persist for 10 to 14 days in children. RVs have been identified in several studies as the second most common viral infection identified in association with bronchiolitis after RSV. (54)(55) An infection with either RSV or RV that results in a wheezing illness during the first year of life is an independent risk factor for wheezing later in childhood. (56)(57) When RV is identified as the sole pathogen in a transplant recipient with lower respiratory tract infection, it can cause severe pneumonia with a clinical picture similar to that of influenza-associated pneumonia. (58)

The availability of multiplex PCR assays has revolutionized the diagnosis of RV. Because RVs have many nucleotide sequences in common among the RNA genomes of the various serotypes, especially in the noncoding region at the 5′ end, the PCR assays have been designed and widely used for the detection of RVs, often in panels with other respiratory viruses. Some assays do not distinguish RVs from enteroviruses, whereas others are RV specific. (59)(60) Prolonged shedding can confound interpretation of a causal role in clinical settings (45) and is common in infants younger than 3 months.

There is no effective treatment available for "RV colds." Intranasal administration of interferon-α to the family members after symptoms appeared in the index case prevented 80% of the secondary RV cold cases. (61) The disadvantage of interferon-α prophylaxis is prolonged administration (>7 days needed) and repeated treatment produces an inflammatory response manifesting as nasal stuffiness, ulceration, and blood-tinged discharge. A capsid-binding agent, pleconaril, has in vitro antiviral activity against many enteroviruses and RVs, and phase 3 clinical trials on naturally acquired colds demonstrated some reduction in the severity and duration of several respiratory symptoms. (62)

Antihistamines, decongestants, and antitussives have not been shown to be effective in children with colds. (63) Development of a vaccine is hindered by the large number of serotypes and the serotype specificity of immunity.

Summary

- Respiratory syncytial virus (RSV) and influenza account for most of the cold weather infections. Other important viruses responsible for respiratory infection in children include parainfluenza virus (peak in fall and spring), human metapneumovirus (peak in late winter and fall but activity is seen throughout the year), respiratory adenovirus (throughout the year), and rhinovirus (year-round with peak in cold weather).
- Based on strong clinical evidence, (5) RSV is the most common cause of bronchiolitis in infants and young children.
- Based on expert and consensus opinion, (2) clinicians should not routinely obtain radiologic or laboratory studies in cases of bronchiolitis. In addition, clinicians should not administer medications such as albuterol, epinephrine, and antibiotics in viral bronchiolitis.
- Based on analysis and interpretation of data, (19) palivizumab should be reserved for high-risk infants such as those born at or before 29 weeks of gestation, infants with chronic lung disease, and infants with congenital heart disease who continue to require treatment for their underlying condition until 24 months of age.
- Based on expert opinion, (24) influenza treatment should be considered in high-risk patients and in hospitalized children, ideally within 48 hours of symptom onset. The antiviral agent of choice is oral oseltamivir.
- Based on strong evidence, (35) parainfluenza 1 and 2 are a major cause of croup in the fall, and primary management is supportive care.
- Based on consensus, (41) the mainstay of treatment in adenoviral infections is supportive care. There is limited evidence (38) for use of cidofovir, even in immunocompromised hosts.
- Based on strong research evidence, (44) human metapneumovirus is a paramyxovirus causing bronchiolitis illness similar to RSV, and there is no antiviral drug therapy available.
- Based on strong evidence, (50) rhinovirus is the most common cause of the "common cold" in children and adults. Its detection in the multiplex polymerase chain reaction may represent infection or asymptomatic shedding.

References for this article are at http://pedsinreview.aappublications.org/content/40/10/497.

PIR Quiz

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1. A 5-week-old boy born at 34 weeks' gestation is brought to the emergency department (ED) by his parents due to a concern of "strange breathing." He has a 1-day history of nasal congestion. His father and 6-year-old brother who live in the home have had a recent upper respiratory tract infection. The family visits a maternal grandmother once a week, and she has recently had a "stomach flu." The baby is noted to have two 15- to 20-second pauses in his breathing while in the ED and is admitted to the hospital. A multiplex PCR from a nasopharyngeal specimen is positive for respiratory syncytial virus (RSV). Which of the following transmission mechanisms is most likely responsible for the RSV infection in this patient?
   A. Direct contact with his brother's nasal secretions.
   B. Fecal-oral transmission from his grandmother.
   C. Large airborne particles from his brother.
   D. Large airborne particles from his father.
   E. Small airborne particles from his father.

2. A previously healthy 4-month-old girl is brought to the ED due to a 3-day history of nasal congestion and increasing cough in the past day. She has felt warm at home and her breastfeeding has progressively decreased during the past day. Her rectal temperature is 100.8°F (38.2°C), respiratory rate is 68 breaths/min, and oxygen saturation on room air is 87%. Bilateral wheezes are heard. After suctioning and supplemental oxygen her oxygen saturation is 96% and her respiratory rate decreases to 48 breaths/min. She is to be admitted to the hospital, which currently has a very high census on the pediatric inpatient service requiring 2 patients to be in the same room (cohorting). Which of the following is the most appropriate next step in management while in the ED?
   A. Chest radiography.
   B. Inhaled hypertonic saline therapy.
   C. Inhaled ribavirin therapy.
   D. Intravenous methylprednisolone therapy.
   E. Nasopharyngeal swab for multiplex polymerase chain reaction.

3. A 2-month-old girl born in September at 26 weeks' gestation is in the NICU. She is no longer intubated but is still on supplemental oxygen. She does not have a history of congenital heart disease. Which of the following is the most appropriate active or passive immunization that this patient must receive at this time?
   A. Inactivated influenza vaccine.
   B. Live attenuated influenza vaccine.
   C. Oral adenovirus vaccine.
   D. Palivizumab prophylaxis.
   E. Ribavirin prophylaxis.

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4. A previously healthy 6-month-old boy presents to the ED with a 2-day history of fever, nasal congestion, worsening cough, decreased activity, and posttussive emesis. Mom states that he is not breastfeeding well and his urine output has decreased. He appears ill but not lethargic. His temperature is 102.4°F (39.1°C), he is tachypneic with subcostal retractions, and his oxygen saturation on room air is 88%. Breath sounds are equal on the right and left with no crackles or wheezes. He is started on supplemental oxygen and his oxygen saturation increases to 94% and his respiratory distress improves. A rapid antigen assay is positive for influenza A. He is admitted to the hospital and is started on intravenous hydration in addition to continuing supplemental oxygen. Which of the following is the most appropriate next step in management?

   A. Chest radiography.
   B. Inhaled albuterol therapy.
   C. Inhaled zanamivir therapy.
   D. Intravenous vancomycin and ceftriaxone therapy.
   E. Oral oseltamivir therapy.

5. A 9-month-old boy presents to the office in September for a health supervision visit. He was born at 38 weeks' gestation and was noted to have a small ventricular septal defect at 2 weeks of age. He has been followed by pediatric cardiology and has not required surgical repair and is taking no medications. At his last visit to the pediatric cardiologist, mom was told that her son would probably not need surgery because the ventricular septal defect would most likely close spontaneously. He is growing and developing well. His examination findings are normal except for a grade 2 systolic murmur on heart examination. The boy has no allergies, but his 7-year-old sister is allergic to eggs. Which of the following is the most appropriate next step in management?

   A. Chemoprophylaxis with oseltamivir from November to April.
   B. Chemoprophylaxis with zanamivir if he is exposed to influenza.
   C. Inactivated influenza vaccine.
   D. Live attentuated influenza vaccine.
   E. Palivizumab therapy.

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