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New and Emerging Infections of the Lung

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Introduction

In this era of rapid globalization and frequent travel, emerging viral infections have gained an immense potential to spread at an unprecedented speed and scale compared with the past. This poses a significant challenge to coordinated international efforts in global surveillance and infection control.

Significantly, respiratory viral infections, spread mostly via droplet transmission, are extremely contagious and have caused significant morbidity and mortality during outbreaks in the last decade. Molecular diagnostics via reverse transcriptase polymerase chain reaction (RT-PCR) have been key in the rapid diagnosis of most of these viral infections. However, a high index of suspicion and early institution of appropriate isolation measures remain as the mainstay in the control and containment of the spread of these viral infections. Although treatment for most of the viral infections remains supportive, efficacious antiviral agents against influenza infections exist.

The infections discussed in this chapter include those first described in the 2000s: Middle East respiratory syndrome coronavirus (MERS-CoV) and metapneumovirus and rhinovirus C as well as those that have been described in the past but have reemerged in the last decade in outbreaks resulting in significant morbidity and mortality, including adenovirus, influenza virus, and enterovirus D68 (EV-D68).

EPIDEMIOLOGY

EV-D68 was first isolated in 1962 in California and had been rare with occasional reports of clusters. Since the late 2000s, EV-D68 has been increasingly reported in various parts of the world. In August 2014, the US Centers for Disease Control and Prevention (CDC) reported cases beginning in the Midwest, with more than 1000 cases reported in 49 states in 2014.1

ETIOLOGY

EV-D68 is a single-stranded, nonenveloped RNA virus. It belongs to the genus Enteroviruses and family Picornaviridae. It is one of the five EV-D serotypes identified so far. It has virologic characteristics including the ability to bind to α-2, 6-linked sialic acids that are present in the upper respiratory tract, which facilitate respiratory infections (Table 28.1).2

PATHOLOGY/PATHOGENESIS

The pathogenesis of EV-D68 has been studied in animal models. Schieble and colleagues noted that the Rhyne strain demonstrated a neurotropic virulence with paralysis of mice. However, despite the predominant respiratory symptoms seen in humans, no effective animal models have been established. Humans are at the moment the only known natural reservoirs of the disease.

CLINICAL FEATURES

The incubation period for EV-D68 is between 1–5 days, similar to many other viral respiratory infections, and the infectious period lasts from a day prior to symptom onset to about 5 days after onset. Spread of infection occurs by droplet transmission and through the fecal-oral route or indirect contact with contaminated surfaces, as with other enteroviruses.

SYMPTOMS

EV-D68 primarily causes acute respiratory symptoms, unlike other enteroviruses. Presenting symptoms range from mild upper respiratory symptoms such as rhinorrhea, sore throat, fever, and rash to severe pneumonia. Most reported cases were associated with difficulty breathing and wheezing, but this may affected by reporting bias.1 Patients can also present with aseptic meningitis or encephalitis. EV-D68 infection has been reported to have a predilection for patients with a personal or family history of atopy.1 The respiratory symptoms have also been reported to be more severe in those with underlying respiratory illnesses such as asthma, often requiring intensive care treatment. Prior to virological diagnosis, many of these cases were often discharged with a diagnosis of asthma exacerbation.

During the outbreak in California and Colorado, a significant group of children was reported to have presented with acute flaccid myelitis, symptoms of sudden asymmetric limb weakness, facial weakness, ophthalmoplegia, or bulbar signs; they were found to be positive for EV-D68 in their nasopharyngeal swabs. However, the spectrum of neurologic disease associated with EV-D68 has not been fully characterized.

PHYSICAL FINDINGS

The physical findings for infected patients are similar to those associated with most respiratory viral infections and
ABSTRACT
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Significantly, respiratory viral infections, spread mostly via droplet transmission, are extremely contagious and have caused significant morbidity and mortality during outbreaks in the last decade. Molecular diagnostics via reverse transcriptase polymerase chain reaction (RT-PCR) have been key in the rapid diagnosis of most of these viral infections. However, a high index of suspicion and early institution of appropriate isolation measures remain as the mainstay in the control and containment of the spread of these viral infections. Although treatment for most of the viral infections remains supportive, efficacious antiviral agents against influenza infections exist.

The infections discussed in this chapter include those first described in the 2000s: Middle East respiratory syndrome coronavirus (MERS-CoV) and metapneumovirus and rhinovirus C as well as those that have been described in the past but have reemerged in the last decade in outbreaks resulting in significant morbidity and mortality, including adenovirus, influenza virus, and enterovirus D68 (EV-D68).

KEYWORDS
emerging infections
virus
respiratory
Table 28.1 Summary Table of Characteristics of Emerging Viral Respiratory Infections

| Virus            | Mode of Transmission | Incubation Period | Clinical Features                                                                 | Diagnosis* | Management and Treatment | Prophylaxis |
|------------------|----------------------|-------------------|-----------------------------------------------------------------------------------|------------|--------------------------|-------------|
| Enterovirus D68 (EV-D68) | Droplet, Fecal-oral, Fomites | 1–5 days | Respiratory, Rarely flaccid myelitis, Predilection to atopic individuals | PCR, Viral cultures (including serum) | Supportive | Supportive |
| MERS-CoV          | Droplet              | 2–14 days, median of 5 days | ARDS, Myalgia, Gastrointestinal, Asymptomatic, Respiratory, Gastrointestinal | RT-PCR (including stool specimens) | Supportive | Supportive |
| Human metapneumovirus | Droplet, Fomites     | 4–6 days | Shedding can last 1–2 weeks, Predisposes to severe bacterial infections | RT-PCR, Immunofluorescence assay (IFA) | Supportive | Supportive |
| Rhinovirus C      | Aerosol or droplet, Fomites | 0.5–3 days | Respiratory, Coinfection with bacterial infections common | RT-PCR | Supportive | Supportive |
| Adenovirus        | Aerosol or droplet, Fomites, Fecal-oral | 2–14 days | Shedding up to 2 years in stool, Pharyngoconjunctival fever, Respiratory, Gastrointestinal, Renal-hematuria | DFA, PCR (throat, sputum and rectal swabs; blood and stool in immunocompromised), Serologic rise in antibody titers | Supportive | Oral vaccine (types 4 and 7) |

ARDS, Acute respiratory distress syndrome; ARF, acute renal failure; DFA, direct fluorescent assay; MERS-CoV, Middle East respiratory syndrome coronavirus; RT-PCR, reverse transcriptase polymerase chain reaction.

*Unless otherwise stated, samples were obtained from the nasopharynx or oropharynx.

**Off-label use.

are not specific to the disease. However, a significant number of EV-D68 patients have been reported with wheezing as the main clinical feature. Patients with more severe EV-D68 respiratory infections present with tachypnea and retractions.1 As already mentioned, neurologic symptoms including flaccid myelitis have also been associated with EV-D68 infections.

IMAGING, PULMONARY FUNCTION TESTS, LABORATORY FINDINGS

Chest radiographs often demonstrate peribronchial thickening and infiltrates, often with areas of atelectasis.4,5

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

EV-D68 can be identified using molecular methods, polymerase chain reaction (PCR), or viral cultures of fluid samples from the nasopharynx, oropharynx, and serum. Most commercially available respiratory multiplex PCR assays may not be able to distinguish enteroviruses from rhinoviruses, so specific assays for EV-D68 may be needed to identify infections with EV-D68 if the clinical suspicion is high.

MANAGEMENT AND TREATMENT

Supportive care remains the mainstay of treatment. No specific treatment is currently available.4 Pleconaril has not been shown to be effective for EV-D68 to date.

PREVENTION

There are currently no available vaccines. Good hand hygiene and prompt diagnosis with subsequent isolation of cases is the main approach to containing the spread of these infections.

PROGNOSIS

Initial studies had suggested that patients with EV-D68 infection, compared with other pulmonary pathogens such as rhinoviruses or non EV-D68 enteroviruses, were more likely to have severe respiratory symptoms and to require hospitalization.1 However, in a more recent retrospective analysis of the outbreak at the St. Louis Children’s Hospital,1 the cases analyzed have shown no significant difference in severity of illness in EV-D68 patients compared with those with other viral etiologies. This may have been due to ascertainment bias, as more severely affected children were tested and thus the case fatality rate appeared to be much higher than it probably really was. This has happened with a number of respiratory viruses, including influenza A H1N1 in 2009, when it was first recognized.

In most cases of EV-D68 infection, with supportive care recovery is expected over a few days. Fatalities have been associated with neurologic complications or occasionally cardiac events.6,7

Middle East Respiratory Syndrome Coronavirus

EPIDEMIOLOGY

First reported in April 2012 in Jordan,8 MERS-CoV spread rapidly to the Middle East, including the Kingdom of Saudi Arabia (KSA), the United Arab Emirates (UAE), and Qatar.
ETIOLOGY

MERS-CoV is an enveloped single-stranded RNA virus belonging to the family Coronaviridae. As with most coronaviruses, the reservoir of infection is thought to originate from animals. MERS-CoV is postulated to have originated from the dromedary camels within the Arabian Peninsula. Molecular isolation of several alphacoronaviruses and betacoronaviruses from bats in Saudi Arabia and other parts of the world has suggested the involvement of bats in human infection as well. The actual route of zoonotic transmission has not been clearly defined despite the publication of a large case-control study.\(^\text{10}\)

PATHOLOGY/PATHOGENESIS

The exact pathogenesis of MERS-CoV is being elucidated. Studies looking at ex vivo infected hepatoma cells demonstrate severe cytopathic effects.\(^\text{11}\) Hocke and colleagues\(^\text{12}\) have demonstrated, through spectral microscopy, significant MERS-CoV antigen expression in type I and II alveolar cells, ciliated bronchial epithelium, and unciliated cuboidal cells of terminal bronchioles as well as pulmonary vessel endothelial cells. Evidence of alveolar epithelial damage with detachment of type II alveolar epithelial cells and associated disruption of tight junctions, chromatind condensation, nuclear fragmentation, and membrane blebbing were seen on electron microscopy.\(^\text{1,2}\) The receptor for MERS-CoV has been identified as dipeptidyl peptidase 4 (DPP4) (CD26), an exopeptidase, which has been demonstrated in cells on spectral microscopy.\(^\text{11}\)

MERS-CoV infection causes significant host immune dysregulation with downregulation of genes involved in the antigen-presenting pathway, leading to subsequent impaired adaptive immune responses, possibly explaining the rapid progression of the illness and the high mortality rate.

CLINICAL FEATURES

Most of the MERS-CoV infections were spread via travel to or residence in countries near the Arabian Peninsula. Infection occurs via droplet transmission from patients to close contacts. The risk of person-to-person transmission is generally low, but superspreading events have been identified similar to the severe acute respiratory syndrome (SARS) coronavirus, in which single individuals have been associated with transmission to large numbers of others. The median incubation period for secondary cases of human-to-human transmission is about 5 days (range 2–14 days).\(^\text{13}\)

SYMPTOMS

In adults, infection results in fever as well as upper and lower respiratory tract symptoms including cough and breathlessness, which can rapidly deteriorate to severe acute respiratory distress syndrome. Other symptoms of myalgia and gastrointestinal symptoms of diarrhea, vomiting, and abdominal pain were commonly present.\(^\text{14}\) However, two case series from the Middle East\(^\text{15,16}\) have reported that MERS-CoV infection ran a milder course in children, with the majority being asymptomatic carriers who were contacts of symptomatic adult cases. Severe respiratory symptoms occurred more commonly in those with existing comorbidities.

The reported patients’ age range has been from below 1 year to 99 years of age, although children have formed a minority of cases. This may be due to limited exposure to animals or health care settings where most infections have occurred.

The respiratory symptoms in symptomatic cases are rapidly progressive, with the median time from onset of symptoms to hospitalization being about 4 days and from onset to intensive care admission for severe cases approximately 5 days. Complications include acute respiratory failure, acute respiratory distress syndrome, refractory hypoxemia, and extra-pulmonary complications (ischemic hepatitis, septic shock, hypotenion, acute renal failure). The median time from onset to death was about 12 days.\(^\text{13}\)

PHYSICAL FINDINGS

Patients presenting with symptomatic MERS-CoV infection have mainly lower respiratory findings, including tachypnea, rhonchi, and retractions, although upper respiratory symptoms have been reported.

IMAGING, PULMONARY FUNCTION TESTS, LABORATORY FINDINGS

Reported chest x-ray findings have included unilateral or bilateral patchy opacities, consolidation, interstitial infiltrates, and pleural effusions.\(^\text{14}\)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Laboratory confirmation of active MERS-coV infection is based on real-time reverse transcription PCR (RT-PCR) detection of at least two specific genomic targets or a single positive target with sequencing of a second target.\(^\text{17}\) Confirmation with nucleic acid sequencing may be required for epidemiologic investigation of the origin and spread of the disease. Specimen collection sites for RT-PCR include lower respiratory samples (bronchoalveolar lavage, tracheal, or sputum aspirates) and upper respiratory samples (nasopharyngeal and oropharyngeal swabs) as well as serum and stool specimens, although the highest yield has been from respiratory samples.\(^\text{17}\)

Serologic testing by enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA) or microneutralization assay is available for the detection of previous infection and is used mainly for surveillance purposes: it should not be used as a diagnostic tool as there is a risk of cross-reactivity with other coronaviruses.
A single negative result on a recommended specimen sent is sufficient to demonstrate no active MERS-CoV infection according to the definition of the US CDC. However, if the clinical suspicion remains, more samples should be sent, as false-negatives do occur.

Patients who have been diagnosed with MERS-CoV are considered clear of active infection and can be deisolated when two consecutive specimen tests are negative on RT-PCR.

Other infectious etiologies presenting similarly with acute, rapidly progressive respiratory distress syndrome include SARS and influenza virus (H5N1). Noninfective causes of acute respiratory distress syndrome (ARDS) should be considered as well. The epidemiologic history and a high index of clinical suspicion are critical.

**MANAGEMENT AND TREATMENT**

No specific antivirals have developed at this point, and the mainstay of treatment remains supportive care.

**PREVENTION**

Currently no vaccine is available against MERS-CoV. Strict infection control measures, including standard, contact, and droplet precautions, with airborne precautions for aerosol-generating procedures, must be taken when care is being provided for suspected or confirmed cases. These have been shown to be effective in controlling nosocomial outbreaks in both the KSA and South Korea. Continued vigilant epidemiologic surveillance, good hand hygiene, and cough etiquette remain the mainstays of prevention for areas not affected by outbreaks.

**PROGNOSIS**

The prognosis is guarded in symptomatic cases, especially in adults, with 3–4 of every 10 patients reported to have died. The number of children infected has been small, so it remains to be seen if the disease runs a more benign course in the pediatric age group. In the adult population, patients admitted to the intensive care unit had a 58% mortality rate at 90 days post admission.18

**Human Metapneumovirus**

**EPIDEMIOLOGY**

Human metapneumovirus (HMPV) was first isolated in pediatric patients with acute respiratory infections in the Netherlands in 2001.19 Subsequent retrospective serologic studies demonstrated the presence of antibodies to HMPV in humans more than 50 years prior;20 and the virus has since been found worldwide. HMPV accounts for up to 10% of viral respiratory tract infections, occurring commonly during the months of January through April in the United States.21 However, a recent 7-year surveillance study in the United States reported that the HMPV season occurred after the respiratory syncytial virus (RSV) and influenza seasons.22 Serologic studies have demonstrated that most children in Europe and North America have acquired a HMPV infection at least once by the age of 5 years.20 Although this is a common childhood respiratory infection, immunity is believed to be transient, and HMPV infection is reported to contribute to acute respiratory illnesses in the elderly (above age 65) who have comorbid respiratory conditions such as asthma or chronic obstructive pulmonary disease or conditions resulting in an immunocompromised status. The overall rate of detection of HMPV was 6% among hospitalized children with respiratory studies.21 Although there have been questions as to whether HMPV is truly a pathogen, asymptomatic carriage among children is estimated to be only 1%.21

**ETIOLOGY**

HMPV is an enveloped single-stranded RNA virus and is a member of the Paramyxoviridae family, belonging to the subfamily Pneumovirinae under the genus *Metapneumovirus*. Two genotypes of HMPV exist, A and B; subgroups are based on the fusion (F) and attachment (G) surface glycoproteins.20

**PATHOLOGY/PATHOGENESIS**

The pathogenesis of HMPV infection has been extensively studied in multiple animal models. Studies on young adult cotton rats inoculated with the virus demonstrate inflammation within and surrounding the bronchi and bronchioles with significant leukocytosis. The HMPV was found mostly on the apical surface of the columnar cells. In the same animal model, upregulation of mRNAs related to interferon gamma (IFN-γ), CCL5, CCL2, CCL3 and interleukin (IL)-2 was demonstrated. Previous infection conferred partial protection in these rats, with lower viral loads within the respiratory tract and a neutralizing antibody response on subsequent infection.21 However, long-term immunity seems unlikely given the incidence of disease in older adults.

**CLINICAL FEATURES**

HMPV infection is transmitted via close or direct contact with contaminated secretions; the incubation period of HMPV is estimated to be 4–6 days.20 The duration of symptoms varies according to severity, but it is commonly less than a week. However, shedding of the virus in infected cases can last from 1 to 2 weeks after the acute illness, with viral RNA found in stools 5 days to 2 weeks after symptom initiation.20 A large prospective surveillance study done by the US CDC on HMPV infection in children21 found that infected children were mostly without comorbidities and most were younger than 5 years of age, with many infants less than 6 months of age. The annual rate of hospitalization associated with HPMV infection was similar to that of influenza virus (1 per 1000) but lower than that for RSV (3 per 1000).19

**SYMPTOMS**

Clinical infection with HMPV results in initial upper respiratory tract symptoms such as cough, rhinorrhea, and fever and can progress to lower respiratory tract symptoms of shortness of breath and wheezing. Sore throat, conjunctivitis, poor appetite, rash, and other gastrointestinal symptoms such as vomiting and diarrhea have been reported.21–25 The
diagnosis is often not made clinically. In a 2-year population-based prospective surveillance study, outpatient cases subsequently found to be positive for HMPV were discharged mostly with the diagnosis of viral illness and bronchiolitis, while inpatient cases were mostly discharged with a diagnosis of bronchiolitis, asthma, or pneumonia. Although infections are usually mild and self-limiting, some studies suggest that HMPV infections can predispose to severe bacterial infections, which complicate the course of the disease.

**PHYSICAL FINDINGS**

Clinical findings in infected cases are like those seen in other respiratory viral infections, although fever was less common in children with HMPV infections than those with influenza in one study. However, findings of respiratory distress, tachypnea, and wheezing were more common in patients with HMPV infections than in those with influenza in the same study.

**IMAGING, PULMONARY FUNCTION TESTS, LABORATORY FINDINGS**

Initial laboratory findings may reveal lymphopenia, neutropenia, and transaminitis, or they may be completely normal. Chest x-ray findings for lower respiratory tract involvement in severe disease, especially in the immunocompromised, have demonstrated ground-glass opacities with parenchymal airspace consolidation, ill-defined nodular-like centrilobular opacities and bronchial wall thickening (Fig. 28.1). Compared with RSV pneumonia, in one series HMPV pneumonia showed more asymmetrical findings.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Diagnostic tests for HMPV infection include various techniques of culture, the nucleic acid amplification test (NAAR), antigen detection and serologic testing. As culturing the virus is technically challenging owing to its slow growth and cytopathic effects in vitro, the most commonly used detection technique is via RT-PCR from nasopharyngeal or oropharyngeal samples. Direct IFA testing can be done in outbreak settings because of the shorter turnaround time, but IFA has a lower sensitivity. Serologic testing has been used mainly for epidemiologic purposes.

Differential diagnoses for similar upper respiratory tract presentations would include other viral etiologies including RSV, influenza, parainfluenza, and adenovirus. In the immunocompromised host with lower respiratory tract signs, fungal etiologies would have to be considered as well.

**MANAGEMENT AND TREATMENT**

Treatment of HMPV infections, like that of other viral infections, is mainly supportive; however, there is much interest in developing therapeutic options. Ribavirin, a nucleoside inhibitor licensed for the treatment of RSV and hepatitis C infections, has demonstrated good in vitro and in vivo activity against HMPV in animal models. Another example is the intranasally administered Human Fab DS7. Standard intravenous immunoglobulin preparations have also been shown to inhibit replication of HMPV in vitro.

RNA interference is a new approach to treating RNA viral infections by regulating gene expression through the silencing of specific mRNAs. Two extremely efficient small interfering RNAs against HMPV have been identified by Deffrasnes and colleagues. These are still in the investigation phase. Finally, Wyde and colleagues have investigated the antiviral properties of sulfated sialyl lipid and heparin and have found activity against HMPV in vitro.

Although there has yet to be a randomized controlled trial on therapeutics in HMPV infections, in severe case, in uncontrolled studies a combination of oral and aerosolized ribavirin with polyclonal intravenous immunoglobulin had some effect.

**PREVENTION**

An effective vaccine against HMPV remains to be developed. Strategic targeting of the F and G surface proteins for both live attenuated and inactivated vaccine development is in progress. Particularly challenging is the fact that natural infection confers only transient immunity and reinfections are common into adulthood. This raises questions about the protective effect of any future vaccine.

Infection control remains the mainstay of prevention, especially within the hospital. Droplet isolation of infected cases with lower respiratory tract symptoms should be implemented until symptom recovery.

**PROGNOSIS**

Although children infected with HMPV had a higher likelihood of supplemental oxygen use and were noted to have a
longer intensive care unit (ICU) stay compared to respiratory infections from other causes, the rates of ICU admission and intubation remained similar to other respiratory infections. The lengths of stay in hospital were not significantly different and fatal HMPV infections are rare.

**Rhinovirus C**

**EPIDEMIOLOGY**

Human Rhinovirus C (HRV-C) is the newest member of the HRV family, having been discovered only in 2006 after retrospective VP4 sequence analysis, done with respiratory samples from patients in Queensland and New York City, showed distinct clustering from known HRV-A and HRV-B species. Shortly after being described, these rhinoviruses were quickly reported worldwide in countries including Africa, Asia, Australia, America, and Europe and are now estimated to contribute to greater than 5% of tested specimens, highlighting their importance as a cause of respiratory tract infections. In Asia and the United States, HRV-C and HRV-A are the most prevalent of the three species. There appears to be a seasonality in HRV-C infections, with a peak incidence in the fall and winter, as well as the rainy season in tropical countries, but also occurring throughout the year. HRV-C infection has a predilection for the young, with most infections occurring in children less than 5 years of age, especially those below the age of 36 months. Part of the apparent rise in rhinovirus C infection may be due to improved virus detection methods that have led to an increase in its recognition as a cause of severe pneumonia in the elderly and the immunocompromised, specifically in pediatric oncology and patients who have undergone hematopoietic stem cell transplantation.

**ETIOLOGY**

HRV-C is a positive-sense, single-stranded nonenveloped RNA virus from the Picornaviridae family. It is one of the three species of HRV based on phylogenetic sequence analysis and is distinctly distinguished from other previously described species (HRV-A and HRV-B) on the basis of genomic features.

**PATHOLOGY/PATHOGENESIS**

In healthy individuals, HRV-C infection mostly causes rhinosinusitis through a neutrophilic inflammatory response resulting in increased vascular permeability and mucus hypersecretion in the upper respiratory tract. Cough, though less common, is thought to be due to direct infection of the bronchi or irritation from the posterior pharyngeal drainage of secretions. In patients with asthma or underlying lung disease, lower respiratory symptoms are more common. Despite the fact that rhinoviruses grow optimally at 33°C, which favors the upper respiratory tract, it is postulated that the warmer temperature in the lower respiratory tract is not an absolute barrier to replication. In many children with pneumonia, rhinoviruses have been isolated together with bacterial pathogens suggesting that HRV infection may lead to a predisposition to other respiratory pathogens. This has been supported by studies demonstrating that human tracheal epithelial cells had increased adherence to Streptococcus pneumoniae when coinfected by HRV. Other studies have also demonstrated that HRV-exposed macrophages had suboptimal responses to bacterial toll-like receptor agonists, which may predispose to secondary bacterial infections in humans.

The true prevalence and pathogenic role of HRVs in the community has not been investigated in detail, and HRV has been found in lower airway fluids and cells of healthy volunteers. Cohort studies, though, have shown high rates of HRV-C detection (up to 75%) in hospitalized children with lower respiratory illnesses.

There are also increasing data linking wheezing secondary to HRV in early infancy with a higher risk of subsequent development of asthma compared with wheezing caused by other viruses. The Childhood Origins of Asthma (COAST) study showed that HRV-related wheezing in the first year of life led to a threefold risk of having asthma at 6 years. HRV wheezing in year 2 was associated with a more pronounced increase in asthma risk (odds ratio [OR] ~7), while HRV-related wheezing during year 3 of life was associated with an even dramatic (OR ~32) increase in asthma at school age. A similar birth cohort study in Australia reported that HRV-related wheezing in infancy was associated with an increased asthma risk at 5 years. The exact mechanisms by which HRV triggers or contributes to the inflammatory changes often seen in asthma is unclear, but it is suggested that it evolves from a combination of host susceptibility, other aeroallergen sensitization and the ability of HRV to activate proinflammatory and airway remodeling pathways.

**CLINICAL FEATURES**

Symptoms of HRV-C infection typically occur after an incubation period of 12–72 hours. The disease is spread through aerosol or droplet transmission or direct person-to-person contact with contaminated secretions. Symptoms generally last 7–11 days.

**SYMPTOMS**

Symptoms of HRV-C infection in children include fever greater than 38°C, and both upper and lower respiratory symptoms of cough, wheezing and shortness of breath. Infections commonly associated with HRV-C include acute upper respiratory tract infection, acute laryngitis, suppurative tonsillitis, otitis media, bronchitis, bronchiolitis, and bronchopneumonia. Although the clinical course is generally mild, HRV-C has been found to be more virulent than HRV-A and can run a more severe course in immunocompromised hosts—for example, children with hematologic malignancies, hematopoietic stem cell transplant recipients, and those on long-term steroid use.

**PHYSICAL FINDINGS**

Common findings in HRV-C infection include upper respiratory tract signs of nasal congestion, cough, facial tenderness with sinus involvement, and inflammation of the tympanic membrane with otitis media. With lower respiratory tract involvement, symptoms such wheezing, cough, and dyspnea are common.
PROGNOSIS
Despite the initial reports of high mortality from rhinovirus C infections, most cases are associated with a good prognosis. A recent study of hematology and oncology patients did not detect any deaths associated with HRV-C infection. In a study from the Philippines, although rhinoviruses were the most common pathogens identified in children hospitalized with pneumonia, there were no fatalities associated with HRV infections, unlike influenza A.51

Adenovirus

EPIDEMIOLOGY
Adenovirus has been recognized as a pathogen since its discovery in 1953. However, recent interest in this virus as an emerging or (more accurately) reemerging respiratory pathogen arose from continued small outbreaks worldwide in both the United States and Asia. These have affected infants and young children, with 90% of them below the age of 60 months.52 Significantly, in Taiwan, there was a noted surge in cases in 2010–2011, triggering the establishment of a national surveillance system that found an acute rise of adenovirus-positive respiratory tract specimens from a baseline of 5.75% to a peak of 37.3% of all respiratory viruses isolated.53 Outbreaks across Asia appear to be linked by molecular epidemiology, although the mode of international spread is not clear.54

ETIOLOGY
Adenoviruses are icosahedral, nonenveloped, medium-sized, double-stranded DNA viruses with more than 50 immunologically distinct serotypes; they belong to the family Adenoviridae. The serotypes linked to epidemic keratoconjunctivitis include types 8, 19, 37, 53, and 54. Those that typically cause acute respiratory disease are types 3, 4, and 7, while the enteric adenoviruses in children are mainly types 40 and 41.55

Adenoviruses are known to be resistant to common disinfectants and can remain on surfaces and in the water of pools and lakes for long periods of time.56

TRANSMISSION AND INFECTION
Adenovirus is spread by droplet transmission of respiratory secretions or direct contact with infected secretions (respiratory, urine, stool, or ocular). The virus can also spread through water and via the fecal-oral route. Shedding of the virus in stools has been documented for up to 2 years after an infection, and shedding can occur in the urine as well. The virus can cause latent infection in lymphoid tissue such as the adenoidal and tonsillar tissues of the throat, but the clinical significance of this is unclear.

CLINICAL FEATURES
The incubation period of adenoviral infections ranges from 2 to 14 days. Infection has been known to cause pharyngitis, adenoiditis, tonsillitis, otitis media, and keratoconjunctivitis.
commonly known as pharyngoconjunctival fever. Lower respiratory tract involvement with pneumonia and bronchitis has also been seen. Adenoviral infections are also known to cause extrapulmonary manifestations, which are commonly seen as acute gastroenteritis and acute hemorrhagic cystitis, with some cases of hepatitis and rarely meningoencephalitis. Infection is particularly severe and prolonged in the immunocompromised, especially those who have undergone hematologic stem cell transplantation.

Certain serotypes, particularly 3, 7, and 21, have been reported to result in epidemics or fulminant events associated with long-term respiratory complications of bronchiolitis obliterans, bronchiectasis, and Swyer–James syndrome. Detection of the virus can be performed via antigen detection, PCR, virus isolation, or serology. Antigen testing by direct fluorescent assay of respiratory secretions (nasopharyngeal) has been shown to have a sensitivity of about 62.5% and a specificity of up to 100%. PCR testing for adenovirus can be done on throat swabs, sputum, and rectal swabs with a reported sensitivity of 91%, 88%, and 86%, respectively. However, pleural effusion fluid has low pickup rates of adenovirus, estimated to be only 39%. Adenoviral PCR on blood and stool samples is most useful for immunocompromised patients in cases with severe manifestations. Blood serologic testing demonstrating a fourfold rise in the antibody titers between the acute and convalescent phases is the gold-standard diagnosis but is less commonly done owing to the development of more rapid diagnostic methods. Serotyping is not routinely performed and is used mainly for epidemiologic surveillance purposes.

SYMPTOMS
The main symptoms of adenoviral infection include fever, cough, rhinorrhea, sore throat, and bilateral conjunctivitis, which can last from 3 to 5 days. Occasionally adenoviral infections cause prolonged fevers. Lower respiratory tract involvement is much less common. Extrapulmonary manifestations include diarrhea, abdominal pain, vomiting, and hematuria.

PHYSICAL FINDINGS
Pharyngoconjunctival fever typically manifests with bilateral conjunctivitis, an injected pharynx and tonsils with significant bilateral cervical lymphadenopathy. In adenoviral pneumonia, findings include significant hypoxia, wheezing, and features of pulmonary consolidation.

IMAGING, PULMONARY FUNCTION TESTS, LABORATORY FINDINGS
Adenoviral infections can easily be confused with bacterial infections, as they are known to cause leukocytosis and neutrophilia on peripheral blood counts as well as elevated inflammatory markers. Transaminitis is also often noted with adenoviral infections. Because of high fevers, which can be more prolonged than with other viral causes, children with adenoviral infections are often presumptively treated for bacterial infections, with blood and urine cultures, and antibiotics before the diagnosis is made.

For patients with lower respiratory tract involvement, chest x-ray findings typically show interstitial pulmonary infiltrates; less commonly, lobar consolidation is seen. Detection of the virus can be performed via antigen detection, PCR, virus isolation, or serology. Antigen testing by direct fluorescent assay of respiratory secretions (nasopharyngeal) has been shown to have a sensitivity of about 62.5% and a specificity of up to 100%. PCR testing for adenovirus can be done on throat swabs, sputum, and rectal swabs with a reported sensitivity of 91%, 88%, and 86%, respectively. However, pleural effusion fluid has low pickup rates of adenovirus, estimated to be only 39%. Adenoviral PCR on blood and stool samples is most useful for immunocompromised patients in cases with severe manifestations. Blood serologic testing demonstrating a fourfold rise in the antibody titers between the acute and convalescent phases is the gold-standard diagnosis but is less commonly done owing to the development of more rapid diagnostic methods. Serotyping is not routinely performed and is used mainly for epidemiologic surveillance purposes.

MANAGEMENT AND TREATMENT

No specific treatment exists for adenoviral infections in immunocompetent individuals, and most infections are self-limited. In immunocompromised hosts, the antiviral agent cidofovir has been used to treat severe infections, and several novel therapies have been explored. The treatment of postadenoviral bronchiolitis obliterans remains largely supportive, with oxygen supplementation and bronchodilators. Corticosteroids would be an ideal theoretical treatment, since bronchiolitis obliterans is largely an immune-mediated inflammatory response, but there have been mixed results. In a study of 31 children, the use of systemic steroids in adenoviral pneumonia did not alter the progression to bronchiolitis obliterans. Case series showing...
possible clinical benefit with intravenous methylprednisolone to treat bronchiolitis obliterans have been limited by small sample sizes and other confounders such as bronchodilator therapy. There have been no large clinical trials of the effectiveness of inhaled corticosteroids in the treatment of bronchiolitis obliterans. There is evidence suggesting that latent adenoviral infection causes eosinophilic airway inflammation, leading to the ineffectiveness of steroid treatment.

PREVENTION

Military recruits in the United States from 1971 to 1999 were routinely vaccinated against adenovirus due to the occurrence of outbreaks. After the cessation of vaccination, more cases became apparent. A new oral live attenuated adenoviral vaccine against types 4 and 7 was approved in 2011 for use in military personnel. However, no vaccine has been used in the general public.

PROGNOSIS

Most immunocompetent individuals recover from the infection with no sequelae. However, severe cases of adenoviral pneumonia have been reported to result in bronchiectasis or bronchiolitis obliterans, and there have been deaths from severe adenoviral lung disease, mostly in patients with major underlying illnesses. Immunocompromised hematology and transplant patients have had fatal outcomes from disseminated adenoviral infections with liver failure, respiratory disease, and disseminated infection. Fatal cases have been associated particularly with serotype 7, but other serotypes have also been reported to be associated with fatalities.

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Access the reference list online at ExpertConsult.com.
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