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Emerging Respiratory Viruses in Children

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KEYWORDS

- Novel influenza A • Influenza C • Middle East respiratory syndrome virus
- Rhinovirus C

KEY POINTS

- Molecular diagnostics have led to the increased identification and recognition of existing and new viruses.
- Mutations and gene reassortment have caused transmission of animal viruses to humans.
- Emerging respiratory viruses can circulate seasonally or year-round as intermittent epidemics, or as outbreaks with subsequent resolution.

INTRODUCTION

Respiratory viruses are a leading cause of pediatric morbidity and mortality worldwide. In the last 15 years, molecular detection and sequencing have led to increased pathogen identification in common respiratory illnesses as well as identification of pathogens during outbreak scenarios. Heightened awareness for these and other emerging viruses is necessary to provide the best care for pediatric patients and to alert public health officials of novel diseases.

NOVEL INFLUENZA A

Background

Seasonal influenza A generally causes a yearly epidemic with variable prevalence based on vaccine efficacy and antigenic drift. Antigenic drift occurs in seasonal influenza due to minor mutations in the viral hemagglutinin (H) and neuraminidase (NA) genes. Antigenic shift occurs because of the ability of the virus to infect multiple

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animals, especially birds, and the ability of the segmented genome to undergo reassortment, mixing different proteins from different viral strains (Table 1). Novel influenza strains are antigenically distinct because of complete exchange of gene segments encoding the H or NA proteins, introducing H and NA variants that have not previously circulated in humans; thus, reassortant viruses have the ability to cause pandemics because of minimal preexisting population immunity. Avian influenza viruses can be passed to humans directly through close contact, or indirectly through another animal host. Because these viruses are adapted to birds, they usually have limited ability to replicate in humans, restricting person-to-person transmission. However, this can be circumvented by either mutation or reassortment with a human virus, as in the pandemic 2009 H1N1, which was a reassortment between avian, human, and swine influenza viruses.[1,2] Initially, reports of novel influenza A viruses centered on cases of H5N1. H5N1 human cases have occurred predominantly in Southeast Asia, the Indian subcontinent, and the Middle East; however, H5N1 has been detected in birds across Eurasia, Indonesia, and North Africa. Newly emerging avian influenza strains, including H7N9 and H10N8, have been identified in patients with poultry exposure in China. Seasonal outbreaks of H7N9 in humans have occurred since 2013, with a recent spike in cases in China.[3] Most cases have been reported in adults.[4] Influenza A H5N1 causes more severe disease and higher mortality in children, whereas person-to-person transmission is more common with H7N9, with nearly half of pediatric cases occurring in secondary clusters.[5] These novel influenza strains retain their preference for avian receptors and are not well adapted for human-to-human transmission.[6] Thus, pediatric cases are less common, likely because of lower rates of poultry exposure in children. Nonetheless, these viruses have been adapted in a controlled setting to be transmissible among mammals[7]; therefore, sustained human-to-human transmission could be possible, placing children at risk.

Clinical Symptoms

The clinical symptoms associated with novel influenza A strains are similar to yearly epidemic strains; however, symptoms are often more severe due to lack of preexisting immunity. Since its reemergence in 2003, fatal reports of H5N1 pediatric cases have been described, including symptoms consistent with acute encephalitis.[8] Compared with seasonal H3N2 and H1N1, H5N1-infected patients had a higher viral load and

Table 1
Differences among the influenza virus species

	Influenza A	Influenza B	Influenza C
Outer membrane proteins (total proteins)	Hemagglutinin and neuraminidase (10)	Hemagglutinin and neuraminidase (11)	Hemagglutinin-esterase fusion (9)
Host	Humans, swine, poultry, other animals	Humans and seals	Humans and swine
Variation	Antigenic shift and drift	Antigenic drift	Antigenic drift
Epidemiology	Able to cause pandemics due to reassortment with associated severe disease	Epidemics, but not pandemics, and severe disease can occur	Rare epidemics with generally mild disease

Adapted from Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th edition. Philadelphia: Elsevier/Saunders; 2015; with permission.

more exuberant cytokine response,[9] and mortalities are approximately 60%.[10] Any cytopenia and/or liver involvement is associated with more severe disease.[11,12] H7N9 infection in humans was first reported in China in 2013. Three patients suffered from rapidly progressive, fatal acute respiratory distress syndrome with multiorgan system failure; 2 were known to have recent poultry exposure. Fever and cough are common symptoms,[13] and similar to H5N1, laboratory findings included cytopenia, elevated liver function tests, and elevated creatinine kinase.[13,14] In 2013, a fatal case of novel H10N8 was reported in a patient with recent poultry market exposure in China.[15] Retrospective testing demonstrated that this was a newly emerged virus with no prior evidence of infection in poultry workers.[16]

Diagnosis

Travel history is important for persons with acute respiratory illnesses, because most novel influenza A viruses occur in Southeast Asia. Although influenza can be detected in cell culture, molecular diagnostics are crucial for the rapid identification of novel influenza viruses. Reverse transcriptase polymerase chain reaction (RT-PCR) can identify a broad range of influenza A strains with subsequent genome sequencing for complete identification of novel strains. Alternatively, RT-PCR primers and probes specific for avian H and NA genes are available.[17]

Prevention and Treatment

A whole-virus influenza H5N1 vaccine was found to be safe in a pediatric population with good antibody responses to both H and NA components.[18] Inactivated H7N9 vaccines are undergoing clinical trials,[19] and viruslike particle vaccine candidates are effective in small animal models.[20] Oseltamivir is recommended for persons infected with novel influenza A viruses, although reports of resistance have been described.[21] Chemoprophylaxis with oseltamivir can be considered based on exposure risk. Oseltamivir chemoprophylaxis is recommended in the highest-risk exposure groups (ie, household or close family member contacts of a confirmed or probable case of novel influenza A) and can be considered in moderate-risk exposure groups (ie, health care personnel with unprotected close contact with a confirmed or probable case).[22] Institution of appropriate isolation precautions is important (**Table 2**).[23]

INFLUENZA C

Background

Although initially identified in 1950, influenza C, a member of the *Orthomyxoviridae* family, is less well described than influenza A and B viruses. Influenza C has 9 viral proteins in contrast with the 10 and 11 viral proteins of influenza A and B, respectively. Unlike influenza A and B, it does not contain the NA outer membrane protein. This difference contributes to unique disease characteristics and important considerations

Table 2
Isolation for emerging respiratory viruses

	Standard	Contact	Droplet	Airborne
Novel influenza A	✓	✓	—	✓
Influenza C	✓	—	✓	—
MERS	✓	✓	—	✓
Rhinovirus C	✓	Consider	✓	—

Data from Refs.[23,50,69]

with respect to antiviral treatment. Similar to influenza B, influenza C does not undergo reassortment and antigenic shift, which is in contrast to influenza A. Influenza C does exhibit antigenic drift, and multiple variants can co-circulate (see **Table 1**). Data suggest that the virus circulates globally, and like other respiratory viruses, infection occurs early in life.[1] Most children infected are less than 6 years old.[24] Influenza C has been rarely identified as a cause of medically attended illness in adults.[25] The prevalence of influenza C is typically less than influenza A, but it can approach influenza B for some years.[26] Although overall rates are low, less than 1% of all respiratory specimens in one study,[24] epidemics do occur in conjunction with replacement of the dominant antigenic group.[27,28] Influenza C circulates primarily during the winter to early summer.[24] Recent studies using molecular detection have suggested that influenza C is more frequent in children than previously recognized.[24,26,28–31]

Clinical Symptoms

Influenza C symptoms are indistinguishable from influenza A and B. In one cohort, almost one-fifth of children with influenza C, predominantly those less than 2 years old, were hospitalized primarily due to pneumonia and bronchiolitis. In the ambulatory setting, upper respiratory tract infections were common. Fever and cough were common symptoms in both groups,[24] and influenza C has been identified as a cause of hospitalized pediatric community-acquired pneumonia.[31] Influenza C has been associated with fewer febrile days and less health care utilization than influenza A or B, suggesting a milder pathogen.[29] Like other influenza types, influenza C has been associated with encephalopathy.[32]

Diagnosis

RT-PCR methods have been used to identify influenza C.[30,33] Viral culture is difficult because of limited cell culture methods. Furthermore, the virus does not display an easily distinguishable strong cytopathic effect like influenza A and B.

Prevention and Treatment

Treatment of influenza C is not well described. Neuraminidase inhibitors are ineffective because of the lack of NA glycoprotein on the outer membrane of the virus. In vitro data suggest that amantadine has activity against influenza C[34]; however, the adamantanes have broad toxicities and are not routinely recommended because of high rates of resistance by influenza A.[35] Currently licensed seasonal influenza vaccines do not contain antigens to influenza C and are not protective. Supportive care is recommended. Droplet isolation should be used for children hospitalized with influenza C infection (see **Table 2**).

MIDDLE EAST RESPIRATORY SYNDROME VIRUS

Background

Coronaviruses (CoV) are a common cause of pediatric respiratory tract disease, accounting for about 15% of common colds. Viruses are classified into different genera (*Alpha*-, *Beta*-, *Gamma*-, and *Deltacoronavirus*). CoVs can infect multiple species, and crossover from animals to humans can lead to outbreaks.[1] Epidemic CoVs have been reported, most notably severe acute respiratory syndrome–associated coronavirus (SARS-CoV) in 2002 to 2003.[36] In 2012, a $\geq$60-year-old Saudi Arabian presented with pneumonia and respiratory failure. A novel *Betacoronavirus*, subsequently termed Middle East respiratory syndrome (MERS-CoV), was identified. Although most of the cases were detected in Saudi Arabia and United Arab Emirates, imported cases to the United States were described.[37] The virus was closely related to bat CoVs.[38]

However, camels were later identified as an intermediary host when zoonotic transmissions occurred,[39] and MERS-CoV seroprevalence was significantly higher among persons with camel exposure.[40] Person-to-person transmission did occur, which led to secondary hospital outbreaks.[41] Although initial reports primarily occurred in adults, likely related to zoonotic and occupational exposures, pediatric cases developed in household contacts.[42]

Clinical Symptoms

Case descriptions of patients with MERS-CoV are primarily in adults and in patients hospitalized with SARS-CoV. In one case series, fever was present in 62% of symptomatic patients, and cough was present in 50%. Upper respiratory tract symptoms were less common with only 19% of subjects having rhinorrhea.[43] Gastrointestinal symptoms, including diarrhea, have been reported. Although initial case fatality rates exceeded 50%,[44] a large number (25%) of patients with laboratory-confirmed infection were asymptomatic in other studies.[43] Data are sparse in children. In one case series of 11 Saudi children with confirmed MERS-CoV, the median age was 13 years (range 2–16 years), older than most respiratory viruses. Only 2 patients had symptoms, and both had underlying medical diseases, a 2-year-old with cystic fibrosis and a 14-year-old with Down syndrome and cardiopulmonary disease. Although the younger child died of respiratory failure, the older child had a relatively uncomplicated hospital course. Pulmonary imaging for both children demonstrated bilateral diffuse infiltrates.[45] In one cohort of household contacts of MERS-CoV-infected subjects, the secondary attack rate was relatively low at 5%. The virus did not have an increased predilection for children, and none of the infected children developed symptoms, suggesting that disease may be worse with primary transmission and/or in adults.[42]

Diagnosis

As with novel influenza A viruses, travel and exposure history are important. Real-time RT-PCR is available for the diagnosis of MERS-CoV, and serologic testing also exists.[46] Viral culture can be performed but requires proper specimen handling and biosafety at level-3 facilities.[47]

Prevention and Treatment

No MERS-CoV-specific treatment exists. In a small retrospective study of adults with severe MERS-CoV, patients treated with oral ribavirin and subcutaneous pegylated interferon alpha-2a had improved survival at 14 days (70% vs 29%). However, 28-day survival was not significantly different (30% vs 17%).[48] Candidate vaccines are being studied; however, most are in the preclinical stage.[49] Airborne and contact precautions are recommended to prevent person-to-person transmission (see **Table 2**).[50]

RHINOVIRUS C

Background

Human rhinoviruses (RV), members of the Picornaviridae family, are leading causes of respiratory illness in children. A new RV species, distinct from species A and B, was identified in 2004.[51,52] Sequencing of the viral protein 4 (VP4) region from specimens of children hospitalized with respiratory illness corroborated the discovery of this new species, rhinovirus C (RV-C). Most children in whom the isolate was identified were hospitalized with asthma or febrile wheeze.[53] Sixty genotypes of RV-C have been identified. The global burden of RV-C is significant with approximately one-quarter of RV infections attributed to RV-C. Rates of RV-C are generally higher

than RV-B and comparable to RV-A in some studies.[54] RV-C is detected year-round.[55,56]

Clinical Symptoms

Although RVs are detected in both symptomatic and asymptomatic children, RV-C is more commonly associated with episodes of clinical illness.[57] Only 3% of RV-C is detected in healthy children.[58] RV-C can cause severe respiratory disease, particularly in asthmatics, and was associated with asthma exacerbations in children in a case-control study.[59] Children with RV-C are more likely to require supplemental oxygen and to have wheezing than children with RV-A.[60] However, in other studies, RV-A and RV-C produce similar clinical symptoms.[55,56] In one case series, 40% of RV-C-infected hospitalized children required supplemental oxygen and 95% wheezed.[56] RV-C-infected children in the outpatient and emergency department settings were more likely to have radiographically confirmed/clinically diagnosed lower respiratory tract illness (eg, bronchiolitis, pneumonia, croup, and asthma) compared with children with other RVs.[61,62] In addition, children with RV-C-related wheezing were more likely to be hospitalized for respiratory problems compared with non-RV respiratory viruses.[63]

Diagnosis

RV is typically detected from nasopharyngeal specimens using RT-PCR. Broad range PCR allows for detection of a variety of RVs by using primers targeting a conserved region. A subsequent step, including seminested PCR or sequencing, can identify the specific species and serotype. RV-C has also been detected in stool[64] as well as in blood, in which higher rates of viremia occurred with RV-C compared with other RV types.[65] RV can be detected using cell culture; however, this method is highly variable and depends on optimal temperatures (33°C–34°C), motion, and time (10–14 days to see cytopathic effect).[1] Furthermore, RV-C is extremely difficult to culture and requires highly specialized methods.[66] Antigen and antibody detection is hampered by the presence of numerous RV serotypes.

Prevention and Treatment

No licensed treatment of RV-C exists. Experimental antivirals have had some in vitro efficacy against RV-C, although notably, pleconaril did not have activity.[67] RV vaccine development has been complicated by the numerous viral serotypes and lack of cross-serotype protection.[68] Droplet isolation should be used for children hospitalized with clinically apparent RV-C infection.

SUMMARY

Respiratory viruses remain a leading cause of childhood disease. The identification and emergence of novel respiratory viruses are important for pediatricians and infectious diseases clinicians. Viruses that were previously difficult to culture can now be rapidly identified using molecular diagnostics and sequencing, and these techniques are highly useful for detecting outbreaks. In addition, the ongoing evolution of viruses and ability to mutate allows for species-to-species transmission of novel viruses. Practitioners should remain on high alert for emerging viruses in cases whereby a cause cannot be identified for a clinical syndrome or if the clinical syndrome is more severe than expected for the identified pathogen. Travel and animal exposure history are important to maintain a high index of suspicion, and rapid institution of appropriate isolation precautions is crucial to prevent person-to-person transmission (see **Table 2**).

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