Viral Respiratory Tract Infections in the Immunocompromised Child

Rachael S. Barr, MRCPCH,† and Simon B. Drysdale, FRCPCH, PhD‡§*

Immunocompromise in the pediatric population encompasses a diverse array of causes and clinical phenotypes. Primary immunodeficiencies are inherited conditions that affect the functioning of the immune system. This may include deficiencies in B-cell or T-cell function, phagocytic function or complement system among others. Secondary immunodeficiencies are those acquired during life caused by factors such as malignancy, immunosuppressive medications, hematopoietic stem cell transplant (HSCT), HIV, malnutrition and significant systemic disease.

Viral respiratory tract infections are common in children and may present a more serious clinical picture in those who are immunocompromised compared with immunocompetent children. Common causative viruses include respiratory syncytial virus (RSV), influenza virus, rhinovirus, adenovirus, human metapneumovirus (HMPV), bocavirus, parainfluenza viruses, coronaviruses, including SARS-CoV-2 and other seasonal coronaviruses. Some viruses that do not typically cause respiratory tract disease in immunocompetent children can do so in immunocompromised children, such as members of the Herpesviridae family.

Clinically, respiratory viral infections may manifest as an upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI) or less commonly as disseminated disease. The overall morbidity and mortality caused by viral respiratory infections in this group is hard to quantify and differs according to the underlying immunodeficiency and the causative agent.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is a ubiquitous viral pathogen that infects almost all children by the time they are 2 years of age. It can cause severe and even fatal disease in both immunocompetent children and those with immunodeficiency. In 2019, it was responsible for 3.6 million hospital admissions with acute lower respiratory tract infection and the deaths of over 100,000 children aged 0–5 years globally.[1]

A recent systematic review found that immunocompromised children are at high risk of severe RSV clinical disease.[2] In children not already hospitalized with their underlying condition, RSV infection was found to result in hospital admission in 28%–58% of cases, with up to 29% of those hospitalized requiring admission to an intensive care unit.[2] The majority of studies that reported on RSV associated mortality in those with immunocompromise found rates to be less than 10%; however, mortality rates as high as 19% have been reported in children undergoing hematopoietic stem cell transplant.[2]

Management of RSV infection is largely supportive; however, some antiviral treatments are available. Ribavirin was the first antiviral medication to be approved for the management of RSV. There are studies that have shown ribavirin resulted in a reduction in progression from URTI to LRTI and a reduction in mortality in children who have undergone HSCT.[3] However, it also has significant toxicities. Intravenous immunoglobulin (IVIG) in combination with ribavirin has also been shown to improve clinical outcomes in adults with HSCT when started before the need for mechanical ventilation.[4] Novel treatments are under investigation,

Accepted for publication January 23, 2023
§Department of Paediatrics, St George's University Hospitals NHS Foundation Trust, London, United Kingdom.
‡Centre for Neonatal and Paediatric Infection, St George's, University of London, London, United Kingdom; and
†School of Cellular and Molecular Medicine, University of Bristol, Bristol, United Kingdom;
*Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, United Kingdom;
From the
S.B.D. had received honoraria from MSD and Sanofi Pasteur for taking part in advisory boards and has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Valneva, MSD and Sanofi Pasteur with fees paid to St George's, University of London. R.S.B. has no conflicts of interest to declare.
Address for correspondence: Simon B. Drysdale, MD, Centre for Neonatal and Paediatric Infection and Department of Paediatrics, St George's University Hospitals NHS Foundation Trust, London, United Kingdom. E-mail: simon.drysdale@nhs.net.

ISSN: 0891-3668/23/00XX-0000
DOI: 10.1097/INF.0000000000003855

with some orally administered antiviral drugs showing promising results in phase 1 and 2 clinical trials.[5]

Prevention of RSV infection is an area that has been extensively investigated over the last few decades. Palivizumab is a recombinant humanized monoclonal antibody (mAb) that targets the fusion (F) protein of RSV. It is licensed for the prevention of RSV infection in certain groups of high-risk children and is administered by monthly intramuscular injections throughout the RSV season. Recommendations for use vary by country; however, eligible groups include infants with severe combined immunodeficiency (SCID).[6,7] Palivizumab does not have a role in the treatment of RSV infection.[7] Other anti-RSV mAbs are in development.[8] There are currently no vaccines licensed for prevention of RSV. The 4 vaccines currently in phase 3 trials are all based on the RSV F protein; however, their target populations vary and include maternal populations and the elderly.

INFLUENZA VIRUS

Influenza virus is a common respiratory virus, which causes seasonal epidemics and can cause severe disease even in immunocompetent children. As influenza A and B viruses cause seasonal epidemics that vary in severity, the incidence of disease and mortality can vary widely in any given setting from 1 year to the next.[9] In 2018, there were estimated to be between 13,200 and 97,200 deaths globally in children under 5 years of age caused by influenza LRTI.[9] Children with immunocompromise have been identified as being at an increased risk of requiring hospital admission caused by influenza.[10] In 2010, in England, the mortality in children and adults with no risk factors was 0.4 per 100,000, and in those with immunosuppression/immunodeficiency was 20 per 100,000.[11]

Management of influenza infection is primarily based around supportive care; however, there are some licensed antiviral treatments. Neuraminidase inhibitors target the surface protein neuraminidase, which is essential for the spread of the influenza virus between cells *in vivo.* Oseltamivir and zanamivir are the most commonly used neuraminidase inhibitors. Their use is recommended by both the UK NICE guidelines and the US CDC in people who are "at risk" including those who are immunosuppressed. Baloxavir marboxil is also licensed in both the United States and EU for treatment of influenza infection in those over 12 years of age. It works by inhibiting cap-dependent endonuclease (CEN), an enzyme important in viral mRNA synthesis. There are a number of other medications currently under investigation.[12] The furthest advanced of these is favipiravir. This is a guanosine analogue that interrupts the virus' ability to effectively replicate and has undergone several phase 3 clinical trials. It is licensed to treat influenza in Japan but currently remains unlicensed in the United Kingdom, EU and United States.

There are 2 types of widely available vaccines for prevention of influenza virus: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV). The vaccines are typically trivalent or quadrivalent and are reformulated annually to predict the strains likely to circulate and cause seasonal epidemics in the coming year. Many countries including the United Kingdom and United States recommend influenza vaccine for all children over 2 years of age.

The LAIV is contraindicated in children with severe immunocompromise caused by the risk of developing influenza infection from the vaccine. Current recommendations, therefore, for immunocompromised children are to offer IIV to all children with immunocompromise who are older than 6 months of age. Children who do not meet the definition of severe immunocompromise but remain in a clinical risk group should be offered LAIV.[11]

SARS-COV-2 AND SEASONAL CORONAVIRUSES

SARS-CoV-2 rarely causes severe disease in children but can lead to significant morbidity and mortality. A meta-analysis of SARS-CoV-2 infection in children showed that immunosuppression increased the risk of death with an odds ratio of 4.93. This is similar to the odds ratio of 4.16 for children with any single comorbidity.[13] Another large prospective study including over 1500 immunocompromised children demonstrated no increased risk of severe disease or death from SARS-CoV-2 infection.[14] Several treatments have been shown in large randomized trials to be efficacious—to varying extents—in treating COVID-19 in adults, including dexamethasone, remdesivir, tocilizumab and baricitinib, and these are now also widely used in children.[15] With so much ongoing research in this area, the evidence base is rapidly evolving and along with it the advice and guidance provided to families of immunocompromised children.

There are a number of vaccines now available for prevention of COVID-19 including mRNA, adenovirus vectored, inactivated viral and protein subunit vaccines.[16]

Other seasonal human coronaviruses (eg, HCoV-NL63, HCoV-HKU1, HCoV-OC43 and HCoV-229E) also contribute to respiratory disease in children.[17] However, the morbidity and mortality caused by these in immunocompromised children are largely unknown and management is supportive.

ADENOVIRUS

There are over 50 serotypes of human adenovirus. Different serotypes demonstrate differing tissue tropisms with respiratory and gastrointestinal manifestations being the most common. Immunosuppression is a risk factor for severe disease with adenovirus, particularly in patients with T-cell lymphopenia and allogeneic stem cell transplantation.[18] Mortality caused by adenovirus is variable depending on the underlying cause of the immunodeficiency. However, reported case fatality rates are as high as 50–60% in disseminated adenovirus infection in the immunocompromised.[18,19] Treatment with the antiviral cidofovir has been shown to reduce morbidity and mortality in these patients.[20]

OTHER VIRUSES

There are a wide range of other viruses that can cause respiratory disease in children. These include, but are not limited to, rhinoviruses, adenoviruses, bocaviruses, parainfluenza and human metapneumovirus. All these viruses are common causative agents of viral respiratory tract infection in children and can cause a wide range of clinical syndromes similar to that of RSV and influenza.

Rhinovirus infections typically peak during the spring and autumn in temperate climates. There have been few studies looking at the impact of rhinovirus infection in immunocompromised patients. One study of rhinovirus infection in HSCT recipients showed a 90-day mortality from upper respiratory and lower respiratory tract infection of 6% and 41%, respectively.[21] Mortality following lower respiratory tract infection with rhinovirus was similar to that caused by RSV and influenza in an adjusted model.[21]

Human parainfluenza virus consists of 4 major serotypes, all capable of causing respiratory disease. Serotype 3 is the most commonly isolated serotype in symptomatic disease in both adults and children.[22] Parainfluenza URTI progresses to LRTI in 40−55% of immunocompromised patients and can result in a mortality rate of up to 37−50%.[22]

As with many of the above pathogens, data on human metapneumovirus (HMPV) in immunocompromised patients are provided mostly by small studies. However, a systematic review of HMPV infection in HSCT and hematologic malignancy patients estimated overall mortality from infection at 6%.[23] However, there was a substantial increase in mortality to 27% in those who developed LRTI.[23]

Human bocavirus (HBoV) 1 is predominantly associated with respiratory tract infection in children and HBoV 2−4 are mainly detected in stool with uncertain pathogenicity.[24] Immunocompromise is a risk factor for severe disease caused by HBoV 1 with

a number of case studies reporting severe disease in these groups.[24]

None of the above viruses have specific management or prevention options and treatment is supportive in nature. Ribavirin and IVIG have both been trialed to treat a number of these viruses; however, their use is not currently routinely recommended. It should be noted that in all these infections, coinfection with bacterial, fungal or other viral pathogens are common, and this contributes to the overall mortality.

NONRESPIRATORY VIRUSES

There are other viruses, which do not typically cause respiratory disease in the immunocompetent host but which can cause severe respiratory infection in immunocompromised patients. Examples include varicella zoster virus and cytomegalovirus. Both can cause severe pneumonitis with significant mortality in immunocompromised children.

CONCLUSION

In summary, there are multiple viruses that can cause respiratory infection in immunocompromised children. The risk of severe and even fatal disease is increased in this population. Despite their almost ubiquitous nature among the pediatric population, very few of these viruses have specific preventative or management measures and more research is needed to reduce the burden they have on immunocompromised children.

REFERENCES

1 Li Y, Wang X, Blau DM, et al. Global, Regional, and National Disease Burden Estimates of Acute Lower Respiratory Infections Due to Respiratory Syncytial Virus in Young Children in 2019: A Systematic Analysis. *Lancet*. 2022;399:2047–2064.

2 Manzoni P, Figueras-Aloy J, Simões EAF, et al. Defining the Incidence and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Children with Chronic Diseases. *Infect Dis Ther*. 2017;6:383–411.

3 Simões EAF, Bont L, Manzoni P, et al. Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children *Infect Dis Ther*2018;7:87–120.

4 Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood*. 2011;117:2755–2763.

5 Hayden FG, Whitley RJ. Respiratory Syncytial Virus Antivirals: Problems and Progress. *J Infect Dis*. 2020;222:1417–1421.

6 Green Book Chapter 27a Respiratory syncytial virus. 2015.

7 Committee on infectious diseases and bronchiolitis committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Am Acad Paediatr*. 2014;134415–420.

8 PATH. *RSV Vaccine and mAb Snapshot*. PATH Vaccine Resour Libr 2021. 2012.

9 Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Heal*. 2020;8:e497–e510.

10 Gill PJ, Ashdown HF, Wang K, et al. Identification of children at risk of influenza-related complications in primary and ambulatory care: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3:139–149.

11 Ramsay M. The Green book of immunisation - chapter 19 influenza. 2020.

12 Davidson S. Treating influenza infection, from now and into the future. *Front Immunol*. 2018;9:1946.

13 Harwood R, Yan H, Talawila Da Camara N, et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. *eClinicalMedicine*. 2022;44:101287.

14 Chappell H, Patel R, Driessens C, et al. Immunocompromised children and young people are at no increased risk of severe COVID-19. *J Infect*. 2022;84:31–39.

15 WHO. *Therapeutics and COVID-19: living guideline*. World Heal Organ. 2021.

16 WHO. *COVID-19 Vaccine: COVID-19 vaccine tracker and landscape*. Available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. 1. 2022.

17 Kuypers J, Martin ET, Heugel J, et al. Clinical Disease in Children Associated With Newly Described Coronavirus Subtypes. *Pediatrics*. 2007;119:e70–e76.

18 Lion T. Adenovirus Infections in Immunocompetent and Immunocompromised Patients. *Clin Microbiol Rev*. 2014;27:441–462.

19 Tylka JC, McCrory MC, Gertz SJ, et al. Immunocompromised Children with Severe Adenoviral Respiratory Infection. *Crit Care Res Pract*. 2016;2016:9458230.

20 Ljungman P, Ribaud P, Eyrich M, et al. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: a survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2003;31:481–486.

21 Seo S, Waghmare A, Scott EM, et al. Human rhinovirus detection in the lower respiratory tract of hematopoietic cell transplant recipients: association with mortality. *Haematologica*. 2017;102:1120–1130.

22 Branche AR, Falsey AR. Parainfluenza Virus Infection. *Semin Respir Crit Care Med*. 2016;37:538–554.

23 Shah DP, Shah PK, Azzi JM, et al. Human metapneumovirus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: A systematic review. *Cancer Lett*. 2016;379:100–106.

24 Christensen A, Kesti O, Elenius V, et al. Human bocaviruses and paediatric infections. *Lancet Child Adolesc Heal*. 2019; 3:418–426.