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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Adenovirus Infections in Immunocompetent Children

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Abstract

Purpose of Review The focus of this review is on human adenovirus (HAdV) infections in immunocompetent children.

Recent Findings HAdV infections are ubiquitous among children under 5 years of age. To date, over 100 different HAdV genotypes have been identified using genomic and bioinformatic analyses. While the vast majority of infections are mild or asymptomatic, severe, life-threatening manifestations including respiratory failure, meningoencephalitis, myocarditis, and disseminated disease can occur in otherwise healthy infants and children. Neonates are at highest risk of severe or disseminated infection, especially within the first 2 weeks of life. Microbiologic diagnosis of HAdV infection is helpful in cases of severe or disseminated disease or in outbreak settings. Molecular detection is the preferred diagnostic method. Evidence for antiviral therapy is limited, but may be warranted in immunocompetent children with severe disease. Hand hygiene, droplet/contact measures, and use of disinfectants are the mainstay for infection prevention in institutional settings. While a live, oral vaccine for types 4 and 7 is available, its use is restricted to military personnel.

Summary HAdV infections in immunocompetent children encompass a wide spectrum of clinical disease. Further research is required in understanding host and viral factors that predispose immunocompetent children to severe infection and to determine what treatments are most effective in those with severe disease.

Keywords Adenovirus · Respiratory viral infections · Viral gastroenteritis · Children · Neonate · Immunocompetent

Introduction

Human adenoviruses (HAdVs) are non-enveloped, double-stranded DNA viruses that measure 70–100 nm in diameter and have a characteristic icosahedral capsid [1••, 2•, 3]. Their name was derived from the word "adenoid," subsequent to their initial detection in surgical human adenoid samples in 1953 [4]. HAdVs can cause a broad range of clinical syndromes in childhood, typically involving the respiratory tract, conjunctiva, or gastrointestinal (GI) tract [1••, 2•, 3]. Severe, life-threatening manifestations such as respiratory failure [5•, 6, 7, 8•], myocarditis [9–11], or encephalitis [12••, 13••], though rare, can occur in otherwise healthy infants and children, with neonates being the most vulnerable [14••]. The purpose of this review is to describe the virology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of HAdV disease in immunocompetent children.

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

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Virology

HAdVs are currently subdivided into 7 species designated A through G within the *Adenoviridae* family [1••, 2•, 3]. Historically, HAdVs were classified as serotypes using traditional serologic methods, serum neutralization, and hemagglutination inhibition assays [1••, 2•, 3]. With recent advances in molecular diagnostics and whole genome sequencing, over 100 distinct HAdV genotypes have now been identified [15–17]. At a species level, HAdVs types tend to display

similar tissue tropisms, which correlate to its disease manifestations [1••, 2•, 3]. HAdV-A, HAdV-F, and HAdV-G are associated with gastrointestinal disease, HAdV-B, HAdV-C, and HAdV-E with respiratory disease, HAdV-C with hepatitis, and HAdV-D with gastrointestinal and ocular disease [1••, 2•, 3]. Table 1 outlines all known HAdV species, serotype/genotypes, and their corresponding sites of predilection. HAdV types 1–51 were identified by serotyping and HAdV types 52–103 were identified by genomic and bioinformatic analyses [1••, 2•, 3, 15].

Epidemiology

HAdV infections are extremely common with most individuals having serologic evidence of past infection by 10 years of age [3, 18]. Approximately, 50% of infections are asymptomatic [21, 34–36], and for the vast majority of those with symptoms, the symptoms are mild and self-limiting [21, 34–36]. Epidemiologic studies conducted in the USA have demonstrated that HAdV account for 5–10% of all febrile illnesses in infants and young children [21, 34–36]. Based on data from the National Adenovirus Type Reporting System in the USA, the most commonly reported types of HAdVs from 2003 to 2016 were HAdVs types 1, 2, 3, 4, 7, and 14, which account for 85.5% ($n = 1283$) of all types reported [37••]. Globally, 1–5, 7, 21, and 41 are the most common types reported to cause human disease in the literature [1••].

HAdV infections can occur endemically throughout the year without seasonality or in epidemics, which tend to occur in the winter and early spring [1••, 2•, 3]. Crowded settings, such as military barracks [38] and college dormitories [39], are well recognized as predisposing to outbreaks. In children, outbreaks in healthcare settings such as hospitals [40, 41], neonatal units [42, 43], and pediatric long-term care facilities [19, 44] have all been well documented, often linked to improper infection control practices [19, 40–44]. Cases of AdV-associated epidemic keratoconjunctivitis (EKC) have been linked to contaminated medical equipment or ophthalmic solutions in ophthalmology clinics [45, 46•]. Outbreaks have also been seen in children in community settings, such as schools [22], daycares [23, 47], and swimming pools [48].

HAdVs are primarily spread via respiratory droplets, conjunctival inoculation, fecal-oral, or fomite transmission [1••, 2•, 3]. Although rare, cases of perinatal transmission have been documented [49, 50, 101]. The incubation period of HAdVs typically range from 2 to 14 days [1••, 2•, 3]. Asymptomatic viral shedding after an acute infection can persist for months and contribute to spread [1••, 3, 21, 34, 35].

Clinical Manifestations

The clinical manifestations of HAdV disease vary widely, ranging from mild to severe focal disease or disseminated disease involving multiple organs [21, 34–36, 102]. Clinical manifestations are influenced by a number of factors including age, immunocompetence, socioeconomic and environmental factors, and HAdV type [1••, 2•, 3]. Table 2 outlines the most common and clinically significant syndromes.

Respiratory Tract Manifestations

HAdV accounts for 5–10% of respiratory tract infections in children [51–53•]. In a large surveillance study of 2638 children in the USA, 15% of hospitalized community-acquired pneumonias in children under 5 years of age were attributed to HAdVs [54]. HAdV-associated upper respiratory tract infections are generally mild and present with fever, coryza, pharyngitis, tonsillitis, tracheitis, or acute otitis media [1••, 3, 23, 55, 56].

Lower respiratory tract infections (LRTIs), such as bronchiolitis and pneumonia, generally present with one or more of fever, cough, tachypnea, wheeze, or shortness of breath [5•, 7, 8•, 23, 24, 53, 54, 57, 58]. Chest radiographs can reveal diffuse bilateral pulmonary infiltrates, similar to other viral pneumonias [5•] or mimic bacterial pneumonia with unifocal or multifocal consolidations [24, 57, 58]. While the vast majority of LRTIs are mild, severe pneumonia, most often associated with types 3, 7, 14, and 21 [1••, 3, 6, 7], can occur,

Table 1 Adenovirus species, types, and predominant sites of infection

Group	Serotype/genotype[a]	Predominant sites of infection
A	[12••, 18–20••]	Gastrointestinal tract, respiratory tract
B	[3, 7, 11, 14••, 16, 21–31]	Respiratory tract
C	[1••, 2•, 5•, 6, 32, 33]	Respiratory tract, liver
D	[8•, 9, 10, 13••, 15, 17, 34–100]	Ocular, gastrointestinal tract
E	[4]	Respiratory tract
F	[101, 102]	Gastrointestinal tract
G	[103]	Gastrointestinal tract

[a] Types 1–51 were identified by serotyping, and all subsequent types (types 52–103) were identified by genomic and bioinformatic analyses

Table 2 Predominant site of infection, clinical syndromes, and key references

Site of infection	Clinical syndrome	Key references
Respiratory tract	Pharyngitis	[23, 52, 55]
	Acute otitis media	[56]
	Bronchiolitis	[5•, 8•, 52, 53•]
	Pneumonia	[4, 5•, 7, 8•, 24, 52, 54]
	Bronchiolitis obliterans	[7, 57, 58]
Ocular	Pharyngoconjunctival fever	[55, 60–62•]
	Epidemic keratoconjunctivitis	[46•, 61–63]
Gastrointestinal	Gastroenteritis	[20••, 66, 68]
	Intussusception	[71•, 72, 73]
	Hepatitis	[75, 76]
Genitourinary	Hemorrhagic cystitis	[28, 29]
	Urethritis	[30, 31]
CNS	Febrile convulsions	[12••, 13••]
	Transient encephalopathy	[80]
	Meningitis	[12••, 13••]
	Meningoencephalitis	[12••, 13••]
	Encephalitis	[12••, 13••]
	ADEM	[12••, 13•]
Other	Myocarditis	[9–11]
	Disseminated disease	[8•, 14••, 102]

predominantly in children less than 5 years of age [54] or in children with comorbidities [5•]. In a review of 44 immunocompetent children with HAdV respiratory infections admitted to a pediatric intensive care unit in the USA, 64% had comorbidities including underlying heart and lung diseases [5•]. Extrapulmonary involvement including rash, diarrhea, hepatomegaly, splenomegaly, and encephalitis can occur concomitantly [59].

While most HAdV-associated LRTIs resolve without sequelae, significant long-term sequelae and even death can occur. Protracted disease often associated with secondary bacterial bronchitis and bronchiectasis has been observed [7, 57, 58, 103]. Furthermore, HAdV is one of the more common causes of postinfectious bronchiolitis obliterans (BO) [7, 57, 58]. In a review of 415 hospitalized children with HAdV-associated LRTIs in Argentina, post-infectious sequelae including BO, bronchiectasis, and chronic atelectasis were observed in 36%, and 15% of patients died [58].

Ocular Manifestations

HAdV ocular manifestations include pharyngoconjunctival fever, epidemic keratoconjunctivitis (EKC), and non-specific conjunctivitis [1••, 3]. Both pharyngoconjunctival fever and EKC are highly contagious and associated with numerous outbreaks in schools [22], swimming pools [48], and hospital facilities [45, 46•].

Pharyngoconjunctival fever is generally mild and self-limiting. It consists of bilateral benign follicular conjunctivitis, fever, pharyngitis, and cervical adenitis [1••, 3, 48, 55, 60, 61]. It can resemble Kawasaki disease [25] and is associated predominantly with types 3 and 7 [1••, 3, 61, 62•]. EKC is more severe and can cause significant morbidity (Fig. 1). After an incubation period of 7–10 days, patients present with unilateral or bilateral conjunctivitis, preauricular adenopathy, and subepithelial infiltrates that are painful and impair vision [1••, 3, 22, 32, 45, 46•, 61]. HAdV types associated with EKC include 8, 19, 37, 53, and 57 [61–63]. EKC may take up to a month to resolve, and corneal opacities may persist for several months to years after infection [64, 65].

Gastrointestinal Tract Manifestations

HAdV generally accounts for 2–5% of acute diarrheal illnesses in young children; however, the prevalence varies widely from country to country [20••, 66]. In low- to middle-income countries, the prevalence of HAdV-associated gastrointestinal disease has been as high as 10–25% [67–69]. Types 40 and 41 are well recognized causes of gastrointestinal disease [26, 47]. However, with the wider use of molecular diagnostics, additional types have occasionally been implicated (i.e., types 52 and 90) [27, 70].

Symptoms of HAdV gastroenteritis include fever, vomiting, and watery diarrhea [67]. After resolution of symptoms, viral shedding in the stool can persist for weeks to months, likely contributing to further spread [21, 34, 35]. In young children, HAdV gastroenteritis has been associated with intussusception [71•, 72, 73]. In a case-control study exploring risk factors of intussusception in infants in Vietnam and Australia, intussusception was strongly associated with HAdV detection in stool specimens, but not with detection of other enteric pathogens, oral polio vaccine, feeding practices, or living conditions [73]. Less common

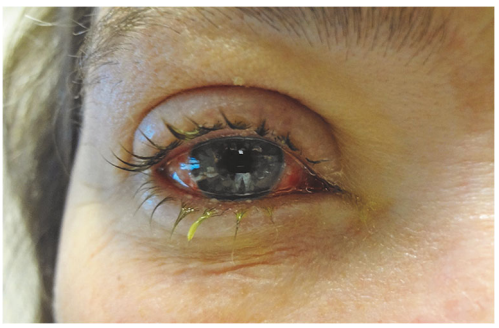

Fig. 1 Epidemic keratoconjunctivitis with crusting lid edema and conjunctival injection (Image copyright Dr. PK Gupta and EyeNet Magazine) [32]

gastrointestinal manifestations include mesenteric adenitis [74], hepatitis [75, 76], and pancreatitis [77].

Genitourinary Tract Manifestations

HAdVs can rarely cause self-limited lower urinary tract infections in immunocompetent children. Clinical manifestations may include dysuria, hematuria, or acute hemorrhagic cystitis [28, 29]. The most common types associated with hemorrhagic cystitis in immunocompetent children are 7, 11, and 21 [28, 29]. HAdV urethritis has also been described in immunocompetent males [30, 31]. In a case-control study of non-gonococcal urethritis, HAdV was the causative pathogen in up to 4% of cases [30]. The most common types associated with HAdV urethritis are 19 and 37 [31].

Central Nervous System Manifestations

HAdV is a rare cause of central nervous system (CNS) disease in immunocompetent children. Two retrospective studies conducted in Canada and Taiwan found that approximately 3% of children hospitalized with confirmed HAdV had neurologic symptoms [12••, 13••]. HAdV type 7 followed by types 3 and 2 were most commonly implicated [12••].

Specific neurologic syndromes associated with HAdV infection include febrile convulsions, aseptic meningitis, transient encephalopathy, encephalitis, meningoencephalitis, myelitis, acute disseminated encephalomyelitis, and Reye-like syndrome [12••, 13••, 78, 79]. Febrile convulsions is most common, accounting for approximately 80% of HAdV-associated CNS manifestations in hospitalized children in one series [12••]. A form of transient encephalopathy, characterized by a decline in level of consciousness after 7 or more days of fever, generalized slowing on EEG, absence of cerebrospinal fluid pleocytosis, and complete recovery over approximately 1 week has been observed [80]. Encephalitis accounts for a minority of HAdV-associated CNS disease cases but is associated with long-term neurologic sequelae and rarely death (Fig. 2) [12••]. Excluding febrile convulsions, potential predictors of adverse outcome from HAdV-associated neurologic disease included younger age (< 2 years old), coagulopathy, and seizures [12••].

Cardiac Manifestations

HAdVs are one of the most common pathogens identified in children with viral myocarditis [9–11]. In two series of acute myocarditis in children, HAdVs were detected by polymerase chain reaction (PCR) in 60% of cardiac samples with myocarditis [9, 10]. HAdV was also implicated as the cause of an atypical febrile syndrome accompanied by acute cardiac decompensation and death in infants and young children in Cuba [11]. In one report relating to this outbreak, 8 of the 11 patients who met the case definition died, and 6 of those 8 subjects had HAdV type 5 detected on post-mortem samples of lungs or myocardium [11].

Other Manifestations

Rare cases of disseminated disease have been described in immunocompetent children and are associated with types 3, 7, 21, and 40 [102]. Disseminated adenoviral disease can affect almost any organ and is diagnosed by detection of HAdV in the blood or in more than one organ site [81, 102]. In a retrospective review of disseminated adenoviral disease in children, 5 of the 11 cases were in immunocompetent children and of those cases, 3 had died [102]. Other rare manifestations include myositis [82], arthritis, [83], and sudden infant death [84].

Neonatal Manifestations

Neonatal HAdV infections are uncommon, as maternal transfer of HAdV antibodies to the fetus is generally protective [49]. When neonatal infections do occur, they can be acquired either vertically [49, 50] or horizontally [14••, 42, 43, 101]. A major risk factor for early onset disease (within 3 days of birth), is a flu-like illness in the mother at the time of delivery or just prior [14••]. In this circumstance, prolonged rupture of membranes may enhance the risk of newborn infection [49, 101]. Severe early onset disseminated HAdV disease in a neonate following a water birth delivery to a mother with active gastroenteritis has been described [101]. Horizontally acquired infections most often manifest after the first week of life. In neonatal intensive care units, such infections have been linked to lapses in infection control practice, such as improper hand hygiene and use of contaminated ophthalmologic equipment [42, 43]. In the largest single series of reported cases, approximately 60% of infected neonates had a documented history of exposure to symptomatic individuals [14••].

Neonatal HAdV infections are associated with significant morbidity and mortality, particularly in those who become symptomatic during the first 2 weeks of life [14, 49, 50, 101]. In a 17-year retrospective review of 26 neonates with adenoviral infection, 21 had disease localized to a single body site or organ system and 5 had disseminated disease [14••]. Those with localized disease presented at a mean age of 18 days (SD 8.1 days) with symptoms compatible with upper respiratory tract infection, bronchiolitis, conjunctivitis, gastroenteritis, or hepatitis. Neonates with disseminated disease presented earlier at a mean age of 7 days (SD 5.2 days); all 5 had severe pneumonia with hypoxemia, hypothermia, and neurologic symptoms such as lethargy or hypotonia; and most had hypotension requiring volume or inotropic support, hepatitis, coagulopathy, and significant laboratory abnormalities including leukopenia, neutropenia, and thrombocytopenia. Four of the 5

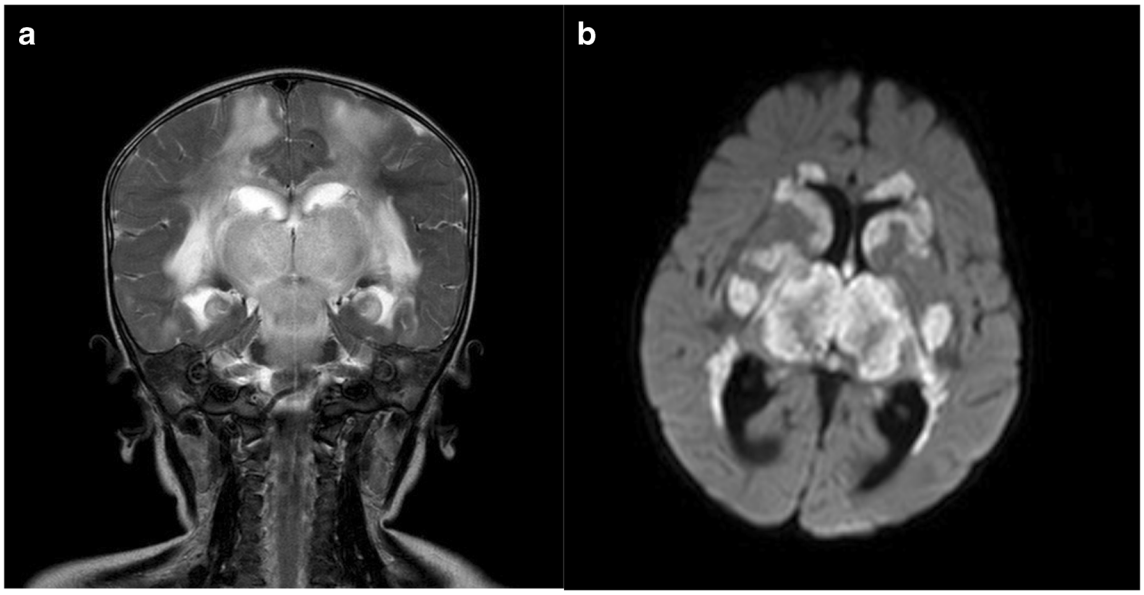

Fig. 2 Magnetic resonance imaging findings in a 10-month-old child with adenovirus encephalitis confirmed by detection of adenovirus serotype 2 by PCR in the nasopharynx, blood, and CSF. **a** Flair coronal image showing extensive enhancement of basal ganglia, midbrain, and periventricular areas bilaterally. **b** Bilateral extensive diffusion of restriction thalami and periventricular areas (Reprinted from Schwartz et al. [12] with permission from Elsevier)

neonates with disseminated disease required extra corporal membrane oxygenation (ECMO) therapy and ultimately died.

Diagnosis

Laboratory diagnosis of HAdV infection is often unnecessary since the vast majority of cases are uncomplicated and self-limiting. Situations in which confirmation of disease may be useful in immunocompetent children, include severe or disseminated disease, and outbreak settings. Diagnostic methods for HAdV include viral culture, antigen detection, and histological and molecular detection methods [1••, 2•]. Molecular detection has become the preferred diagnostic method due to its superior sensitivity and specificity with rapid turnaround time and ability to detect all HAdV types.

Viral culture is seen as the gold standard for detection of HAdV but can lack sensitivity for certain specimens such as peripheral blood [1••]. With the exception of HAdV types 40 and 41, most HAdVs can be readily cultured in human lung carcinoma A549, human embryonic kidney (HEK), and epithelial cell lines such as HEP-2; HAdV types 40 and 41 can only be isolated in HEK 293 cells [85]. The characteristic cytopathic effects seen include grape-like clustering with irregular aggregates and intranuclear inclusions which can be visible within a week of culture, but may take up to 3–4 weeks to develop [1••, 85, 86•]. Viral culture techniques have become less favored due to the relatively slow turnaround time, challenges with specimen transport, and risk of contamination with bacteria or fungi [33].

Direct antigen testing can detect HAdV in respiratory and stool samples with a faster turnaround time compared to viral culture [87] but can only detect common serotypes [88]. Enzyme-linked immunosorbent assay (ELISA) is useful in the detection of HAdV type 40 and 41 in stool samples [33, 89] with an overall sensitivity of approximately 70% compared to viral culture. Furthermore, enzyme immunoassays have lower sensitivity when specimens were collected beyond 5 days of illness onset [86•, 90] and in immunocompromised patients [91]. For respiratory and tissue specimens, immunofluorescence assays have a sensitivity of 28–75% when compared to culture [86•, 92–94].

Histological diagnosis can be made through the detection of intranuclear inclusions termed “smudge cells” which are characterized by enlarged epithelial cells with large nuclei and a thin rim of cytoplasm [85, 95]. Fulminant adenoviral pneumonia is also characterized by cytolytic injury and cellular necrosis of the airway epithelium with mononuclear cell infiltrates and hyaline membrane formation [33].

Conventional qualitative PCR and quantitative real-time PCR (RT-RCR) have a rapid turnaround time [81] and most specimens are suitable for testing including blood. Numerous multiplex panel assays include HAdV and are commercially available for respiratory and stool specimens. These assays demonstrate good sensitivity and specificity (57 to 100% in respiratory samples) [86•], but are generally less sensitive than targeted HAdV PCR assays, particularly when there is lower viral burden within the specimen [86•, 96]. Quantitative RT-PCR assays have been used to monitor HAdV viremia and response to antiviral treatment [86•, 97, 98]. Currently, most

evidence regarding the use of quantitative assays stems from the experience in pediatric transplant recipients. For immunocompetent children with severe HAdV disease, there is a potential role for using quantitative RT-PCR in monitoring clinical course and response to treatment.

Treatment

Adenoviral infections in healthy children are generally uncomplicated and seldom require treatment beyond supportive care. Infants and children with compromised immune systems and those with severe disseminated disease may warrant antiviral therapy; however, there is currently no US Food and Drug Administration (FDA)-approved drug for HAdV disease. Various medications have been used in clinical practice (Table 3), but evidence is limited.

Cidofovir

Cidofovir (CDV) is a cytosine nucleotide analogue with broad spectrum antiviral effect [99]. The phosphorylated active component, cidofovir diphosphate, inhibits viral DNA polymerase, thus terminating adenoviral DNA chain elongation. Efficacy has been demonstrated in in vitro studies [100, 104] and in vivo in AdV-infected mouse models [105]. There are no prospective control trials investigating the efficacy of CDV in HAdV infection, but retrospective studies and case series in immunocompromised patients suggest that it may be effective. Some studies have demonstrated improved survival outcomes by more than 30% in BMT recipients [106–108]; however, effectiveness is not consistently demonstrated [109]. Small number of case reports using CDV in severely infected immunocompetent children suggest that early treatment initiation may lead to faster recovery [87, 110–113]. A recent retrospective study reviewed 85 predominantly immunocompetent children with severely HAdV disease; 17 were treated with CDV, 41% of whom died despite treatment [8•]. It is difficult to draw any strong conclusion from these reports due to small numbers, lack of controls, and potential publication bias.

CDV has also been used in healthy young military recruits with severe HAdV-related respiratory illness [114••, 115, 116, 117]. Out of the 103 military recruits who were treated, 88 required intensive care support, and 9 required ECMO. One study evaluating the efficacy of early CDV treatment (within 7 days of admission) compared with late treatment [114••], concluded that early treatment significantly reduced the development of respiratory failure (13% vs 67%), ICU stay (6 vs 10 days), and hospital length of stay (22 vs 35 days). Nephrotoxicity, characterized by acute kidney injury, proteinuria or a Fanconi-type syndrome, is seen in up to 50% of patients. Other potential adverse effects of CDV include myelosuppression with neutropenia and rarely uveitis [33, 88].

Brincidofovir

Brincidofovir (BCV; CMX001 from Chimerix) is an oral lipid conjugate derivative of cidofovir. It is an oral prodrug with good bioavailability [118]. The lipophilic component also allows the drug to cross the blood-brain-barrier [118–120•] and achieves higher intracellular levels than CDV [121]. Most of the BCV treatment data comes from the transplant population. A Phase II, randomized, placebo-controlled trial demonstrated that BCV as pre-emptive therapy in pediatric and adult BMT

Table 3 Antiviral medications targeting human adenoviruses

Medication	Mode of action	Comment
Cidofovir	Cytosine nucleotide analogue	• Case reports and case series suggest some benefit in immunocompetent, severely ill children • Nephrotoxicity and myelosuppression are relatively common • Co-administered with oral probenecid may reduce nephrotoxicity
Brincidofovir	Oral lipid conjugate derivative of cidofovir	• No studies in immunocompetent children • Can readily cross blood-brain-barrier • Less renal and bone marrow toxicity than cidofovir • Gastrointestinal side effects common
Ribavirin	Guanosine nucleoside analogue	• Efficacy against HAdV type C in vitro • No clear clinical evidence • Can cause hemolytic anemia
Nitazoxanide	Inhibits viral protein synthesis	• Limited reports on efficacy in diarrheal disease in transplant recipients • Some in-vitro data showing inhibition of HAdV • Side effects include headaches, abdominal pain, and nausea

recipients with asymptomatic adenoviremia had lower rates of HAdV disease and lower all-cause mortality when compared to placebo [122]. Preliminary results from the AdVise Trial (Identifier:NCT02087306, ClinicalTrials.gov) demonstrated that 76% of pediatric BMT recipients achieved a significant reduction or clearance of adenoviremia by 4 weeks, even in the absence of complete immune recovery and increased survival in those who responded to treatment [123]. When used as salvage therapy for immunocompromised children or adults who experienced CDV-failure, 66% achieved > 10-fold decrease in viral load after 1 week, and 70% achieved a ≥ 99% decrease from viral load baseline by 8 weeks [88, 124]. There are presently no data on the use of BCV in immunocompetent children. Unlike CDV, BCV generally does not cause nephrotoxicity or myelosuppression [120•]. Diarrhea, nausea, vomiting, and anorexia are the most common adverse effects [120•, 122]. Since May 2019, Chimerix discontinued all ongoing trials involving oral and intravenous BCV due to low patient accrual, but indicated that the drug will still be available for patients with severe HAdV disease as part of an expanded access initiative [125].

Other Therapies

Ribavirin [14••, 100, 102, 126] and nitazoxanide [88, 127] have also been used as treatment in HAdV disease with unclear efficacy (Table 3). Intravenous immune globulin (IVIG) has been used variably as adjunctive therapy for HAdV disease in immunocompetent children [5•, 7, 14••, 111••]. In the largest retrospective case series of neonates with adenoviral infection, 6 out of the 26 infants were treated with IVIG in addition to antiviral therapy. Five of the 6 infants had disseminated disease and 4 out of the 6 infants died [14••].

Adenovirus-specific adoptive T cell transfer (ATCT) has been a relatively recent experimental treatment with encouraging outcomes in pediatric BMT recipients [128]. ATCT was used in one premature infant (29 weeks gestation) who contracted HAdV species C horizontally from the mother [129•]. The infant progressed to severe disseminated disease despite CDV and IVIG treatment. Maternal adenovirus-specific haploidentical T cells were infused on the rationale that there would be maternal immunity; clinical and virologic response was observed within 2 days with clearance of viremia by 2 weeks.

Prevention and Vaccines

In institutional settings, strict hand hygiene and droplet/contact precautions for infected patients are paramount in preventing the spread of HAdV [88]. HAdVs are fairly resistant to many disinfectants and can survive on environmental surfaces for up to 3 months [1••, 3, 130, 131]. The virus can be inactivated by heat, formaldehyde, and chlorine [132], and disinfectants approved by United States Environmental Protection Agency should be used [133]. In the community, appropriate chlorination of swimming pools is important in preventing the spread of pharyngoconjunctival fever [134].

A HAdV vaccine was developed by the US military because of large scale outbreaks that were associated with significant morbidity and mortality among military recruits. The FDA-approved vaccine is a live, oral, enteric-coated vaccine comprising of HAdV types 4 and 7 (responsible for most outbreaks) [135, 136••]. It is licensed for use in military personnel aged between 17 and 50 years. The vaccine is 99% effective and contributed to a dramatic decline in outbreaks within 2 years of its introduction in 2011 [135]. The vaccine is not recommended for children or the general public due to the risk of viral shedding in stool and risk of community transmission [136••].

Conclusion

HAdV infections in immunocompetent children encompass a wide spectrum of disease ranging from mild upper respiratory tract infection, gastroenteritis, and conjunctivitis to severe life-threatening conditions such as pneumonia, myocarditis, encephalitis, and disseminated disease. Neonates who become infected during the first 2 weeks of life are at particularly high risk of disseminated disease and death. Treatment with antiviral medications may be warranted in some immunocompetent children with severe disease. However, these medications are not currently FDA-approved and the evidence for their use is limited. Novel immune therapies are on the horizon and may have a treatment role in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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