Adenovirus infections

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Abstract

Adenoviruses are endemic, primarily causing respiratory and ocular (pharyngoconjunctival fever) symptoms and gastroenteritis infections in infants and children. They also cause epidemic keratoconjunctivitis, pneumonia in military recruits and severe, life-threatening infections in transplant recipients. The hardy non-enveloped virus resists environmental degradation and is transmitted by aerosolized droplets, fomites and faecal-oral spread. Outbreaks occur in medical, day care, military and other facilities where people live in close proximity. Diagnosis is predominantly by nucleic acid amplification technology. Molecular species identification and typing are not used in routine clinical practice, but are important for investigating outbreaks and as research tools. Most infections are subclinical or self-limiting when symptomatic, but adenoviruses cause significant morbidity and mortality, especially in paediatric haemopoietic stem cell transplant (HSCT) recipients. No effective treatment is available. Routine viral load surveillance of high-risk HSCT patients is advocated, with high or increasing levels of viraemia prompting, where possible, a reduction in immunosuppression as first-line management. The antiviral agent cidofovir, is active against adenoviruses *in vitro*, but is not licensed for this indication. Pre-emptive therapy with cidofovir may reduce plasma viral loads, but whether it reduces mortality is less certain. It remains to be seen whether brincidofovir, the oral pro-drug of cidofovir, currently under development, will be effective in pre-empting severe or fatal disease.

Keywords Adenovirus infections; brincidofovir; cidofovir; haemopoietic stem cell transplantation; keratoconjunctivitis; MRCP; pharyngoconjunctival fever; pneumonia viral

Key points

- Adenoviruses principally cause self-limiting respiratory and gastrointestinal infections in the under-5s and conjunctivitis in all age groups
- The capacity for environmental persistence, and innate resistance to standard decontamination procedures, can make outbreaks difficult to control
- Adenoviruses cause substantial morbidity and mortality in transplant recipients, especially in children undergoing haemopoietic stem cell transplant
- Although viral load surveillance can predict severe end-organ disease, only reduction of immunosuppressive dosage, and possibly cidofovir, can pre-empt disease
- Brincidofovir, the new oral lipid ester derivative of cidofovir, offers the best prospect for improved management and prevention of adenovirus disease in transplant recipients

Structure and classification

Adenoviruses take their name from their 1953 discovery in human adenoid tissue grown *in vitro*. The family Adenoviridae are non-enveloped, icosahedral, non-segmented, double-stranded DNA viruses around 35 kbp in size. Apical fibres projecting from capsid surface mediate attachment to host cells. Adenoviruses use either the coxsackie B virus-adenovirus receptor (CAR) or CD46 as their primary receptor. Both are expressed in a broad range of cell types, facilitating multiorgan infection and disease.[1] The 70 or more human adenovirus types belong to the genus *Mastadenovirus* and are classified into seven phylogenetic species, A–G. Species vary in receptor usage, tropism, clinical manifestations and propensity for latency. Broad tissue tropism and the capacity to induce cellular immunity led to the continuing development of adenoviruses as vectors for vaccine and gene therapies.

Epidemiology and transmission

Adenovirus infections are endemic worldwide, primarily causing self-limiting febrile illnesses in young children. Most people have serological evidence of infection with multiple serotypes by age 10 years.[1] The incubation period ranges from 2 days to 2 weeks depending on the virus type and mode of transmission.

Adenoviruses can be spread by droplet inhalation, fomites, the faecal-oral route, and in transplant tissue. Even among non-enveloped viruses, adenoviruses are unusually stable, even in adverse environmental conditions, persisting for a month or more.[2] Relatively resistant to lipid disinfectants, hand decontamination requires 70–90% ethanol hand gels, with formaldehyde or bleach (sodium hypochlorite) for surfaces.[2] Outbreaks have been reported in ophthalmology clinics and other medical facilities, nurseries, swimming pools and cramped living conditions.

Endogenous virus is also a potential source of infection. Reactivation of latent virus in the tonsils, adenoids or gut-associated lymphoid tissues can give rise to asymptomatic virus shedding, and to disease in immunocompromised hosts.[1,3]

Clinical syndromes

Clinical manifestations vary according to age, immunological status and adenovirus type. Up to 50% of infections are

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asymptomatic.[1] The most common manifestations are upper and lower respiratory tract infections and gastroenteritis (infants, children), and viral conjunctivitis (adults, children) (Table 1). Severe or disseminated adenovirus disease can occur in immunocompromised individuals, especially in paediatric haemopoietic stem cell transplant (HSCT) recipients.[3]

Respiratory

Adenoviruses cause up to 10% of fevers in infants, and a significant proportion of upper respiratory tract infections (common cold, pharyngitis, otitis media) in children.[1] Adenoviruses can cause exudative tonsillitis mimicking group A streptococcal infection, and a coughing illness with lymphocytosis similar to pertussis. They are implicated in 10% of cases of childhood pneumonia, with the risk of subsequent bronchiectasis.[1] Routine pneumococcal vaccination has been associated with a reduced incidence of adenovirus pneumonia, suggesting dual pathology. Pneumonia in immunocompetent adults is very rare, but outbreaks occur among US military recruits living in close quarters and subject to strenuous exercise.

Ocular

Benign follicular conjunctivitis can occur at any age, or in association with fever and pharyngitis (pharyngoconjunctival fever) in children. Epidemic keratoconjunctivitis is the most severe manifestation (Figure 1). Unilateral, then bilateral, conjunctivitis with pre-auricular adenopathy is accompanied by corneal involvement with painful subepithelial opacities. Blurred vision can persist beyond the usual 1–3 weeks.

Gastrointestinal

The species F adenoviruses 40 and 41, discovered in stool by electron microscopy, account for a significant proportion of endemic diarrhoea in infants and children. A role for adenoviruses in intussusception and mesenteric adenitis remains unproven.

Other disease associations

Adenoviruses have been associated with acute self-limiting haemorrhagic cystitis, especially in boys, and with urethritis in adults. They can cause acute myocarditis in children and heart transplant recipients. Rare reports implicate adenoviruses in

Adenovirus diseases: age, host, virus types, overall contribution to disease and test samples[1,3,4]

Focus	Condition	Age/host	Type	% of conditions	Sample site for NAAT
Respiratory	Upper respiratory tract infection/pharyngitis[a]	Infants, young children	1–7	5% of URTIs in children	NTS
	Pneumonia	Infants	1–3, 7	15% of pneumonias in infants, and 3% in those >5 years	NTS NPA BAL
	Acute respiratory disease	Adult military recruits	4, 7, 14, 21	Rare outbreaks in military recruits	NTS BAL
	Pertussis-like syndrome	Children	5	–	NTS
Ocular	Pharyngoconjunctival fever	Children	3, 4, 7	65–90% of viral conjunctivitis in adults and children	Conjunctival swab
	Follicular conjunctivitis	Any age	3, 4, 11		
	Epidemic keratoconjunctivitis	Adults	8, 37, 43, 54, 64		
Enteric	Gastroenteritis	Infants, young children	40, 41	2–15% of acute diarrhoeal illnesses in young children	Stool
Genitourinary	Cervicitis, urethritis	Adults	19, 37	Rare	Urine
	Haemorrhagic cystitis	Infants, young children	11, 34, 35	20–70% of haemorrhagic cystitis in children	
Cardiac	Myocarditis	Children	7, 21	Up to 20% of cases of myocarditis in children	Myocardial tissue
Immunocompromised host	Disseminated disease	HSCT	1, 2, 5, 11, 31, 34, 35	6–28% child 0–6% adult HSCT have viraemia	EDTA blood NTS, stool
	Meningoencephalitis	Children HSCT	2, 6, 7, 12, 32		CSF
	Nephritis, haemorrhagic cystitis	HSCT, renal transplant	11, 34, 35		Urine
	Gastrointestinal/hepatitis	HSCT, liver transplant	1–3, 5, 7		Stool Liver biopsy

BAL, bronchoalveolar lavage; CSF, cerebral spinal fluid; HSCT, haemopoietic stem cell transplant; NAAT, nucleic acid amplification technology; NPA, nasopharyngeal aspirate; NTS, throat (and nose) swab; URTI, upper respiratory tract infection.

[a] Can be indistinguishable from group A streptococcal infection with exudate.

Table 1

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