Chapter 6
Adenovirus

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Adenovirus Infection

Etiology

Adenoviruses are nonenveloped, double-stranded DNA viruses. Their lack of a lipid bilayer envelope renders them remarkably stable to inactivation by detergents and other chemical agents, allowing them to remain infectious in the environment for prolonged periods of time. Human adenoviruses are classified into six groups, A through F. More than 79 serotypes have been identified. The vast majority of illnesses caused by adenoviruses are associated with mild-to-moderate respiratory and/or gastrointestinal symptoms. Disease morbidity is highest in young children, immunocompromised individuals, military recruits, and other groups living in crowded conditions. Lethal infection is uncommon, but well described, particularly among certain high-risk populations.

Epidemiology

Approximately 80% of all adenovirus infections occur in children less than 4 years of age. Other populations at high risk include military recruits and those with immunocompromising conditions. Adenoviruses circulate worldwide causing endemic and sporadic infections throughout the calendar year, with epidemics reported most commonly during late winter, spring, and early summer. Disease prevalence in the general population is difficult to determine with precision, since most illnesses are

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self-limiting and not reported. Adenoviruses account for more than half of all acute respiratory infections in military recruits worldwide where close living conditions and stressors related to training cause frequent, large outbreaks. The efficient spread of infection associated with crowded living conditions is also problematic in refugee and displacement camps of war-torn regions, where poor sanitation further exacerbates the problem.

Globally, circulating adenovirus serotypes differ region to region, and change over time. Serotypes 1 through 7 are responsible for more than 80% of infant and childhood infections, while infections caused by serotypes 1 through 5, 7, 14, and 21 are associated with the greatest morbidity. In Asia, a 30% mortality rate has been reported in children less than 3 years of age during outbreaks caused by serotypes 3 and 7. Among military recruits, disruptive outbreaks of moderate-to-severe respiratory infections are most commonly attributed to adenovirus serotypes 4 and 7. Significant outbreaks have also been described from serotypes 3, 11, 14, 17, and 55.

In the USA, the Centers for Disease Control and Prevention tracks adenovirus disease activity using two passive, voluntary, laboratory-based surveillance systems. Since 1989, the National Respiratory and Enteric Virus Surveillance System (NREVSS) has tracked and summarized adenovirus positive laboratory test results according to specimen type (e.g., respiratory sample, blood, urine, cerebrospinal fluid) and the geographic location where the sample was collected. NREVSS does not collect clinical or demographic data, or information related to virus serotype. In 2014, the National Adenovirus Type Reporting System (NATRS) began tracking demographic, clinical, and laboratory data, including virus serotype, on laboratory samples testing positive for adenovirus. The objectives for such enhanced surveillance included timely recognition of outbreaks according to virus serotype, and monitoring for serotype-specific trends in disease severity and geographic spread. Between 2003 and 2016, 1497 adenovirus positive samples were reported from 32 states and the US Virgin Islands. The distribution of adenovirus serotypes that were detected by year is shown in Fig. 6.1. The relative frequency of serotype detection during this 13-year surveillance period is shown in Fig. 6.2. Serotypes 1, 2, 3, 4, 7, and 14 were the most commonly detected serotypes, together accounting for 86% of all identified adenoviruses.

Transmission

Adenoviruses are remarkably stable to inactivation with many chemical and physical agents allowing for prolonged infectivity on environmental surfaces in homes, residence halls, military barracks, schools, hospitals, and others. They resist ultraviolet radiation and tertiary treatment procedures performed on urban wastewater. They are fairly resistant to standard concentrations of common household disinfectants, so industrial or industrial strength disinfectants such as 1% sodium

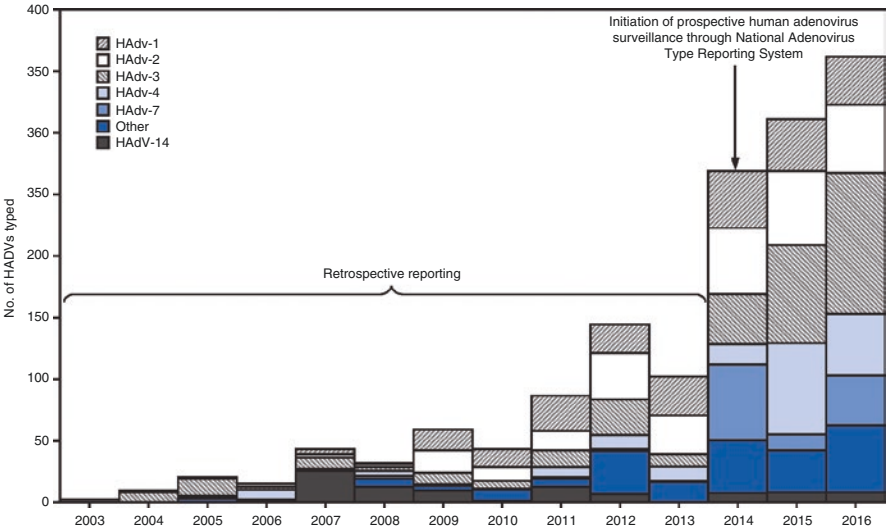

Fig. 6.1 Distribution of human adenovirus species (HAdVs) and types, by year of specimen collection. National Adenovirus Type Reporting System, 32 US states and the US Virgin Islands, 2003–2016. (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/mmwr/volumes/66/wr/mm6639a2.htm. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

hypochlorite, 2% glutaraldehyde, 0.25% sodium dodecyl sulfate, or 95% ethanol solution must be used (Environmental Protection Agency List G disinfectants). They are also inactivated by heat or formaldehyde.

Transmission can occur from person to person or following exposure to a contaminated environmental source. Person-to-person transmission via direct contact or exposure to contaminated respiratory droplets is common. Self-inoculation from touching one's mouth, nose, or eyes after contact with a contaminated fomite (e.g., a doorknob) also occurs regularly. Adenovirus serotypes that are shed from the gastrointestinal tract are easily transmitted via the fecal-oral route. Serotypes 4 and 7 are transmitted quite efficiently via swimming pool or lake water. Ongoing asymptomatic infection of tonsils, adenoids, and intestines is fairly common among immunosuppressed individuals who can shed virus for prolonged periods of time. Transmission is especially efficient in settings where individuals have frequent and prolonged periods of close contact such as in hospitals, newborn nurseries, psychiatric centers, long-term care facilities, boarding schools, college dormitories, orphanages, day-care facilities, job-training centers, public swimming pools, and military barracks. Outbreaks can quickly escalate to epidemic proportions. Following exposure, adenoviruses have an average incubation period of 5–8 days, with a range from 2 to 14 days.

HAdV species	HAdV type	No. (%) of detections
A	12	t3 (0.2)
	31	3 (0.2)
B	3*	341 (22.8)
	7*	127 (8.5)
	11	6 (0.4)
	14*	89 (5.9)
	21	34 (2.3)
	34	2 (0.1)
	35	14 (0.9)
C	1*	248 (16.6)
	2*	293 (19.6)
	5	56 (3.7)
	6	20 (1.3)
D	8	54 (3.6)
	15	1 (0.1)
	19	1 (0.1)
	22	1 (0.1)
	29	1 (0.1)
	37	12 (0.8)
	56	1 (0.1)
E	4*	185 (12.4)
F	41	5 (0.3)
Total	22	1,497 (100)

*One of the six most common types detected, accounting for 1,283(85.5%) of reprts.

Fig. 6.2 Number and percentage of human adenovirus (HAdV) detections, by species and type. National Adenovirus Type Reporting System, 32 states and the US Virgin Islands, 2003–2016. (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/mmwr/volumes/66/wr/mm6639a2.htm. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

Clinical Presentation

Infections of the Respiratory Tract

Adenoviruses cause a broad array of clinical illnesses. Specific disease manifestations depend on the tissue tropism of the infecting serotype and various host factors. A majority of serotypes target the respiratory tract. As a group, adenoviruses are responsible for up to 10% of acute respiratory tract infections in children and between 1% and 7% in adults.

Symptoms associated with infection of the respiratory tract may include fever, cough, red eyes, nasal congestion, sore throat, ear pain, shortness of breath,

headache, and fatigue. Manifestations can be consistent with common cold, keratoconjunctivitis, pharyngoconjunctival fever, pertussis syndrome, otitis media, tonsillopharyngitis, laryngotracheobronchitis, bronchitis, bronchiolitis, or pneumonia. Children may also develop concomitant gastrointestinal symptoms. Symptoms of acute adenovirus infection typically last up to 10 days. Pneumonia develops in up to 20% of infected newborns and infants, but is uncommon in immunocompetent adults. As many as 30% of infected immunocompromised individuals will develop pneumonia with severe respiratory failure. Fatality rate from adenovirus pneumonia in this high-risk population exceeds 50%.

Persistent infection of the lung in previously healthy adults and in those with associated chronic obstructive pulmonary disease has also been described. Adenovirus pneumonia occurs relatively frequently in military recruits. Approximately 25% of those who develop pneumonia require hospitalization for pneumonia. Adenovirus serotypes 4 and 7 are responsible for a majority of these cases.

Infections of the Eye

Infections caused by adenovirus serotypes 3, 4, 7, 11, and 14 may be associated with uncomplicated viral conjunctivitis. The eyes are bright red from the conjunctival hyperemia, but vision is not affected and the infection is self-limiting after 10–14 days. In contrast, epidemic keratoconjunctivitis, caused by adenovirus serotypes 8, 19, 37, 53, 54, and 56, lead to a gritty feeling in the eye with watery discharge, photophobia, and associated redness. Corneal involvement affecting visual acuity can persist for months. Outbreaks of epidemic keratoconjunctivitis have been described originating from day-care facilities, schools, outpatient clinics, chronic care facilities, and hospitals. Nosocomial transmission can occur via contaminated ophthalmic instruments or eye drops.

Infections of the Gastrointestinal Tract

Adenovirus-associated acute gastroenteritis is fairly common in children under 2 years of age. The clinical triad of fever, vomiting, and watery diarrhea is common, with the diarrhea persisting for 1–2 weeks. Most of these infections are caused by adenovirus serotypes 40 and 41. Very rare complications include hemorrhagic colitis, hepatitis, cholecystitis, and pancreatitis.

Infections of Other Organ Systems

Adenovirus infections beyond the respiratory and gastrointestinal tracts are uncommon.

Acute viral hemorrhagic cystitis mimics bacterial urinary tract infections. Serotype 11 is most commonly implicated.

Severe disseminated disease can be seen in newborns and in individuals with immunocompromising conditions. In newborns, disseminated adenovirus infection can cause meningitis, myocarditis, hepatic dysfunction, viral sepsis, and death. Similar complications have been described in immunocompromised children and adults. Between 10% and 30% of hematopoietic stem cell transplant patients who develop a respiratory tract infection with adenovirus will go on to develop disseminated infection. In this context, fatality rates up to 70% can be seen.

Management

No specific treatments for adenovirus infections are available. Symptoms that occur with mild-to-moderate infection, such as fever and pain, can be relieved using over-the-counter medications. The antiviral medication cidofovir is used to treat severe infections in immunocompromised individuals only.

Adenovirus Vaccine

The live bivalent adenovirus serotype 4 and 7 vaccine is approved for use by the US Food and Drug Administration (FDA) in military personnel, aged 17 through 50 years. The vaccine is required by the US Department of Defense for all military recruits entering basic training, and recommended for other high-risk military personnel. Its labeling indication is specifically for the prevention of acute febrile respiratory disease caused by human adenovirus serotypes 4 and 7. In the USA, the vaccine is only available for military personnel through the Department of Defense. The safety and efficacy of the vaccine have not been studied in the general population or in immunosuppressed individuals. Adenovirus vaccines are not currently available for civilian use anywhere in the world.

Vaccine Characteristics

The live adenovirus serotype 4 and 7 vaccine is manufactured by Teva Pharmaceuticals. It was licensed by the FDA in March 2011. The vaccine is a live virus product administered orally in the form of two enteric-coated tablets, one of each containing adenovirus serotype 4 and 7. Following ingestion of the vaccine, replication-competent virus is shed in stool, and can theoretically be transmitted to others. Each tablet contains at least 32,000 tissue-culture infective doses of virus. The vaccine may be given at the same time as other vaccines as necessary. Prior to use, it should be stored under refrigeration at temperatures between 2 °C and 8 °C. The vaccine should never be frozen.

Immunizing Antigen

Strains of adenovirus serotypes 4 and 7 are grown in WI-38 human-diploid fibroblast cell cultures maintained in Dulbecco's Modified Eagle's Medium, fetal bovine serum, and sodium bicarbonate. Virus is harvested, filtered to remove cellular material, formulated, and then lyophilized. The vaccine strain viruses are not attenuated.

Vaccine Additives and Excipients

Tablets contain monosodium glutamate, sucrose, D-mannose, D-fructose, dextrose, human serum albumin, and potassium phosphate. The inner tablet core contains anhydrous lactose, microcrystalline cellulose, potassium, magnesium stearate, and replication-competent live adenovirus. The outer tablet contains microcrystalline cellulose, magnesium stearate, and anhydrous lactose. The enteric-coating contains cellulose acetate, alcohol, acetone, and castor oil. The serotype 7 tablet also contains FD&C (Food, Drug and Cosmetic approved) Yellow#6 aluminum lake dye.

Vaccine Recommendations

The live bivalent adenovirus serotype 4 and 7 vaccine licensed for use in the USA is required by the US Department of Defense for all military recruits entering basic training, and recommended for other high-risk military personnel. Civilian access to the vaccine is not available. Both tablets should be swallowed whole at the same time without crushing or chewing them.

Contraindications to Vaccine

Like all other medical products, a known severe allergy to any component is a contraindication to using the bivalent adenovirus serotype 4 and 7 vaccine.
Like other live vaccines, bivalent adenovirus serotype 4 and 7 vaccine is contraindicated for use during pregnancy. Females of reproductive potential should have a pregnancy test performed prior to receiving the vaccine.

Warnings and Precautions for Vaccine Use

Warnings and precautions for vaccine use include individuals with weakened immune systems due to medical conditions, transplantation, radiation, or drug treatments. Females should avoid becoming pregnant for 6 weeks after vaccination.

Scheduled vaccination should be postponed for individuals with symptoms of vomiting or diarrhea, because vaccine effectiveness depends on multiplication of vaccine virus within the gastrointestinal tract during normal transit time. The vaccine strain viruses are shed in the stool from day 7 up to day 28 post vaccination. Attention to handwashing and personal hygiene is essential to prevent spread to others. This is especially important for household contacts less than 8 years old, those who are pregnant, and those with immune-compromising conditions.

Side Effects and Adverse Events

During clinical vaccine trials, potential side effects are monitored by collecting all reported adverse events (AEs) from all study subjects for a period of time, typically for 1 or 2 weeks following each dose of the study vaccine. If the vaccine is approved for use, these rates are included in the vaccine's package insert. The side effects reported are therefore temporally related to receiving vaccine, but may not be causally related to it. Since phase III efficacy trials, by design, include a control group of individuals that receive either the standard-of-care vaccine or placebo, it is important to compare the rates of AEs between the 2 groups to determine whether the rates of reported side effects are different between the 2 groups.

During clinical trials, recipients of the bivalent live adenovirus serotypes 4 and 7 vaccine reported the following AEs during the 2 weeks following administration of the vaccine: headache (33%), nasal congestion, sore throat, or joint pain (17%), abdominal pain, cough, or nausea (14%), diarrhea or vomiting (10%), and fever (1%). Rates in placebo recipients were almost identical. Rare reports of hypersensitivity reactions, anaphylaxis, and Guillain-Barre syndrome were also reported, but no causal relationship was identified.

Vaccine Efficacy

Results from a 2006 phase III, double-blinded, placebo-controlled, randomized clinical vaccine trial that included 4040 military recruits showed a vaccine efficacy of 99.3% (95% CI: 96.0%, 99.9%) in preventing adenovirus serotype 4 infection. No cases of adenovirus serotype 7 infection were identified in study subjects whether they received vaccine or placebo, so efficacy against serotype 7 infection could not be determined.

Serotype 7 immunogenicity, however, showed that 93.8% of vaccine recipients seroconverted, while only 5.3% of placebo recipients seroconverted.

A postlicensure evaluation of real-world vaccine effectiveness showed that routine vaccine implementation led to a reduction in adenovirus serotypes 4 and 7 infections from a baseline of 5.8 cases per 1000 person-weeks down to 0.02 cases per 1000 person-weeks.

The live bivalent adenovirus serotype 4 and 7 vaccine is safe and highly effective in reducing morbidity associated with adenovirus infections among military recruits. Other high-risks groups for serious infection with adenovirus include newborns, young infants, and individuals who are immunosuppressed. New approaches to adenovirus vaccine development would be necessary to target these groups for immunization, since replication-competent (live), nonattenuated vaccines should not be administered to these patient populations.

References and Suggested Reading

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