

CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

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Adenovirus

INTRODUCTION

The adenoviruses are common pathogens of humans and animals. The Adenoviridae family is composed of double-stranded DNA viruses classified into seven species (A–G), and over 60 human adenovirus serotypes have been described, and are a common cause of viral infections in all age groups at any time of year. Adenoviruses most commonly cause respiratory illness. The illness can range from mild to severe disease including the common cold to pneumonia, croup, and bronchitis. Depending on the type, adenoviruses can cause other illnesses such as gastroenteritis, conjunctivitis, cystitis, and, less commonly, neurological disease. Adenoviruses are mainly transmitted by droplets, the faecal–oral route and fomites. Preventive measures include use of masks, hand hygiene, avoiding close contact & sharing of objects, practicing respiratory etiquettes and isolation during illness.

EPIDEMIOLOGY

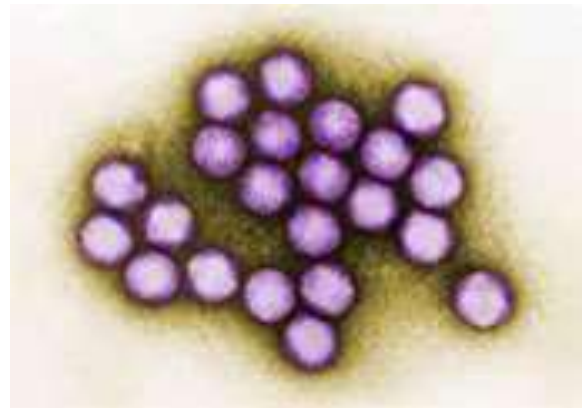
Global & Indian Scenario:

Adenoviruses have a worldwide distribution and infections occur without seasonality. Adenovirus infection accounts for up to 10% of respiratory infections in children. In the last 10 years, instances of severe illness and death from adenovirus type 7 infection have been reported in the United States.

In India, according to the ICMR-NICED, the current spike in cases of acute respiratory infection due to Adenovirus in West Bengal can be attributed to a combination of strains 3 and 7 of the adenovirus.

In Delhi, at ABVIMS & Dr RML hospital adenovirus was found in 13.5% of the respiratory samples tested from the admitted paediatric patients during Jan – March 2023. Of the positive cases, 45 % were co-infected with one or more respiratory viruses namely Human Rhinovirus, Respiratory Syncytial Viruses, Parainfluenza viruses, Metapneumovirus and H3N2.

Agent: Human adenoviruses (HAdVs) are members of the Adenoviridae family. The name derives from the initial isolation of the virus from human adenoids in 1953. Adenoviruses are medium-sized (70–100 nm), nonenveloped double-stranded DNA viruses with an icosahedral nucleocapsid.



Colorized transmission electron micrograph of adenovirus Picture courtesy: CDC

Currently, there are 104 different HAdV types known, which have been classified into seven species A to G based on the percentage of guanine plus cytosine in their DNA and other biochemical and biophysical criteria. The majority of HAdV types belong to species D (73 types) followed by species B (16 types), and new adenovirus types continue to emerge.

Adenovirus infection in humans are generally caused by Adenoviruses types B, C, D, E and F. Specific serotypes are often associated with clinical syndromes. Adenovirus types 3, 4 and 7 are most commonly associated with acute respiratory illness. Adenovirus types 4 and 7 have been associated with more severe outcomes than other adenovirus types, particularly in people with weakened immune systems.

Host: Children and immunocompromised patients or those with existing respiratory or cardiac disease, are at increased risk for infection. Adults who are in closed or crowded environments, are also at higher risk.

Incubation period: The incubation period for Adenovirus is 2–14 days.

Period of communicability: Adenovirus infections are most contagious during the first few days of symptoms. Sometimes the virus can be shed (released from the body) for a long time after a person recovers from an adenovirus infection, especially among people who have weakened immune systems. This “virus shedding” usually occurs without any symptoms, even though the person can still spread adenovirus to other people.

Transmission: Adenoviruses are usually spread from an infected person to others through

- close personal contact, such as touching or shaking hands
- through the air by coughing and sneezing
- touching an object or surface with adenoviruses on it, then touching your mouth, nose, or eyes before washing your hands
- contact with stool, for example, during diaper changing
- Adenovirus can also spread through water of swimming pools and small lakes.

CASE DEFINITION

There is no separate surveillance for adenoviruses and the surveillance for the clinical presentation of the infection in the form of ILI or SARI is done through IDSP. Limited testing for Adenoviruses by ICMR as part of the pan-respiratory virus surveillance is also undertaken.

Probable: ILI (Influenza Like Illness) - Any person with

- an acute respiratory infection (sudden cough and sore throat) with measured fever of $\geq 38^{\circ}\text{C}$ (≥ 100.4 F); with onset within the last 10 days
- SARI (Severe Acute Respiratory infection-Any person with:
 - an acute respiratory infection (sudden cough and sore throat) with measured fever of $\geq 38^{\circ}\text{C}$ (≥ 100.4 F); with onset within the last 10 days
 - AND
 - Requires hospitalization

Confirmed: A presumptive case of ILI or SARI with

- Conventional PCR or real-time PCR
- OR

- Any validated nucleic acid-based test.

CLINICAL FEATURES

Adenoviruses are the most commonly cause of respiratory illness. The illness is usually self-limiting and can range from common cold (or flu), fever to pneumonia, croup, and bronchitis. Adenoviruses can cause a wide range of illnesses (Box 1) including epidemic keratoconjunctivitis (EKC), which is a severe and highly contagious form of viral conjunctivitis (pink eye), acute gastroenteritis (causing diarrhoea, vomiting, nausea, and stomach pain) and the less common illnesses include bladder infection or inflammation & neurologic disease. Acute hepatitis, in previously healthy children, reported from around the world (20 countries) is under investigation. The most frequent causes of acute hepatitis including hepatitis viruses A–E, have been ruled out. More than 20 children have required liver transplants, and several have died. The main suspect is adenovirus (subtype 41) as around 70% have tested positive for the same.

Box 1: The various infections caused by the Adenovirus along with common HAdV type involved are given below:

- 1. Upper respiratory tract**
 - a. Upper Respiratory tract infections- HAdV Type 1, 2, 3, 5, 6, 7
- 2. Lower respiratory tract**
 - a. Acute Bronchitis – HAdV Type 3, 7, 21, 60
 - b. Broncholitis obliterans- HAdV Type 2, 3, 7, 21
 - c. Pneumonia- HAdV Type 1, 2, 3, 4, 5, 7, 7a, 8, 11, 14, 14p1, 21, 35, 55, 56
- 3. Gastrointestinal tract**
 - a. Gastroenteritis – HAdV Type 1, 2, 3, 5, 7, 11, 12, 15, 17, 31, 32, 33, 40, 41
 - b. Childhood diarrhea- HAdV Type 12, 31, 40, 41
 - c. Intussusception – HAdV Type 1, 2, 3, 5, 6, 7, 40, 41
 - d. Appendicitis – HAdV Type 1, 2, 7
 - e. Mesenteric lymphadenitis- HAdV Type 1, 2, 3, 5, 7,
 - f. Hepatitis- HAdV Type 1, 2, 3, 5, 7
- 4. Eye**
 - a. Follicular conjunctivitis- HAdV Type 1, 2, 3, 4, 6, 7, 8, 9, 10, 1, 15, 16, 17, 19, 20, 22, 31, 34, 37
 - b. Pharyngoconjunctival fever- HAdV Type 1, 2, 3, 4, 5, 6, 7, 7a, 8, 14, 37
 - c. Epidemic conjunctivitis – HAdV Type 2, 3, 4, 5, 7, 8, 10, 11, 13, 14, 15, 16, 17, 19, 23, 29, 37, 54, 56
 - d. Hemorrhagic conjunctivitis- HAdV Type
- 5. Central Nervous System**
 - a. Meningoencephalitis- HAdV Type 1, 2, 3, 4, 5, 6, 7, 11, 12, 26, 32, 41
- 6. Cardiovascular System**
 - a. Myocarditis – HAdV Type 7, 21
 - b. Dilated cardiomyopathy
- 7. Urinary Tract**
 - a. Hemorrhagic cystitis- HAdV Type 7, 11, 21, 34, 35
 - b. Nephritis- HAdV Type 3, 4, 7a, 11
- 8. Other organ systems**
 - a. Arthritis- HAdV Type 7
 - b. Thyroiditis-Unknown
 - c. Skin exanthem- HAdV Type 3, 4, 7, 7a
 - d. Hemophagocytic lymphohistiocytosis- HAdV Type 3, 7, 11

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Coinfections of Respiratory viruses like Influenza, SARS-COV-2, RSV, HMPV, Adenovirus, Rhinovirus, Parainfluenza viruses have been reported as dual or even triple infections with several combinations and are postulated to modulate morbidity and mortality, although this association of coinfection and higher severity of disease is not very clear.

Coinfections may be a cause for concern since they may alter the disease severity and epidemiology influencing the risks of outcomes like hospitalization, ICU admission, mechanical ventilation, mortality especially in patients with co-morbidities, immunocompromised status, elderly and paediatric patients. Some studies have also suggested the complexity and challenge in treatment of viral co-infections since antivirals are available for only some respiratory viruses wherein treatment of one virus may negatively influence the dynamics of the other coinfecting virus.

Several factors like sequence of infections, time interval between the exposure with the coinfecting viruses, route of infection has been hypothesized to influence the pathogenicity of such coinfections.

The process of viral interference in coinfections have been suggested to either competitively inhibit replication of other coinfecting virus, enhance its replication or have no effect on its replication.

Host immune response is also believed to influence the outcome of viral coinfections including heterologous immunity, in which a variety of immune cells may induce either a protective or immunopathological response.

Therefore, the possibility of existence of coinfections should be kept in mind while managing respiratory viral infection cases as coinfections with two or more respiratory viruses may be associated with adverse clinical outcomes and therefore have therapeutic and prognostic implications.

DIAGNOSIS

Molecular species identification and typing are not used in routine clinical practice because most people have mild or no symptoms, and no specific treatment is available, but are important for investigating outbreaks, or if one has severe illness or pneumonia and as research tools.

Laboratories can detect and type human adenoviruses using:

- Molecular detection (e.g. PCR)
- Partial or full genome sequencing
- Antigen detection
- Virus isolation
- Virus neutralization with type-specific antisera

Diagnosis is predominantly carried out by nucleic acid amplification technology such as PCR test on respiratory samples and blood.

Molecular assay can be utilized for diagnosing adenoviruses at the serotype level in a broad range of patient specimens, including conjunctival, nasopharyngeal, stool, blood, and urine specimens.

Human adenovirus can be detected through PCR assays with high sensitivity and all the existing serotypes of human adenovirus can be determined by targeted sequencing of the HVR-7 of the hexon gene using the sanger sequencing method.

This molecular assay is expected to contribute for rapid diagnosis and further understanding of epidemiology and disease management.

Health professionals should:

- consider adenoviruses as possible causes of upper respiratory infection, lower respiratory infection such as pneumonia, and conjunctivitis (individual cases or outbreaks)
- report unusual clusters (e.g., respiratory, conjunctivitis) potentially caused by adenoviruses to the state or local health departments

Collecting and Handling Specimens

The types of specimens collected for human adenovirus detection depend on the patient's clinical presentation and type of infection. To improve human adenovirus detection, the specimens should be collected within a week of symptom onset.

Respiratory Infections

For respiratory infections, upper respiratory specimens such as a nasopharyngeal swab and/or oropharyngeal (throat) swab are collected. If there is evidence of a lower respiratory infection, a lower respiratory specimen such as sputum is collected. In some instances, a serum specimen may be helpful

Eye Infections

If there is clinical evidence of a conjunctival or eye infection, a conjunctival swab is collected.

Blood specimen Collected in purple top EDTA tube (whole blood, plasma) or serum; whole blood is preferred to plasma or serum

Stool specimen (or rectal swab in VTM/UTM); whenever possible, a stool specimen is preferred to a rectal swab.

MANAGEMENT

There is no specific treatment or approved antiviral medicine for people with adenovirus infection. Primary Prevention is the mainstay.

Clinical care of adenovirus infections includes treatment of symptoms and complications. Most adenovirus infections are mild and may only require care to help relieve symptoms.

Rest, plenty of fluids and over-the-counter pain medicines or fever reducers are advised to help relieve symptoms. To categories treatment:

1. In immunocompetent host with mild to moderate disease: It consists primarily of supportive care. One is advised to maintain proper hydration, anti-pyretic for fever, anti-emetic for vomiting, oxygen support in case of pneumonia or ARDS, and bed rest.
2. In immunocompetent host with severe disease: No proven role of anti-viral therapy

has been established. Still the pre-emptive treatment is followed with supportive care to the organs involved.

3. In immunocompromised patients: These group of patients mainly include those with solid organ transplants and stem cell transplants. Cidofovir is the only recognized anti-viral agent used. It is mainly used in stem cell transplant. Dosage: 1mg/kg intravenous twice weekly or 5mg/kg every one to two weeks. Adverse effect is nephrotoxicity.
4. IVIGs plus Cidofovir have also been used in stem cell transplants patients which is giving promising results.

For epidemic conjunctivitis, a cold compress and lubricants may provide some relief of discomfort. Patients who are seriously ill with persistent high fever, breathing problems, change in vision, severe dehydration etc. may need care in the hospital to help them recover.

PREVENTIVE MEASURES

Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy. These include:

Non- pharmaceutical Interventions-(NPI)- NPIs include both actions that individuals and households can take (e.g. frequent hand washing, covering coughs and sneezes, and keeping a distance from sick people).

Personal NPIs include:

- **Masking** provides an extra layer of protection against viral illnesses and are strongly recommended in crowded places.
- **Hand hygiene-** Wash hands regularly, and as soon as possible after sneezing or coughing. Use soap and water and wash for 20 seconds. Use an alcohol-based hand sanitizer if one can't wash hands with soap and water.
- Avoid sharing cups, glasses and cutlery with people who are sick. Regularly wash or wipe

down utensils and surfaces with a household cleaner that contains soap or detergent.

Respiratory etiquettes: Cover nose and mouth with a tissue when coughing and sneezing or use elbow. Don't use hands. Dispose of tissues straight away in a bin. Do not spit in public places.

- **Isolation:** Stay at home if one feels unwell so he/she doesn't pass their virus to other people.

Environmental non-pharmaceutical interventions

Adenoviruses are resistant to many common disinfectants and can remain infectious for hours on environmental surfaces and medical instruments. To prevent spread of adenoviruses, use of recommended & registered disinfectants like quaternary ammonium, hydrogen Peroxide, paracetic acid and hypochlorous acid on surfaces that is effective at killing adenoviruses and compatible with the surfaces and equipment is advised. Disinfectants effective against norovirus should also be effective against adenoviruses. Refer guidelines of Infection Control Practices.

Maintain proper chlorine levels to prevent outbreaks: It is important to keep adequate levels of chlorine in swimming pools to prevent outbreaks of conjunctivitis caused by adenoviruses.

In health care settings:

PPE: Use of appropriate personal protective equipment (PPE) when caring for patients.

BMW: Correct containment and disposal of contaminated waste (e.g., dressings) in accordance with Biomedical Waste Management guidelines for infectious waste.

Airborne control measures include ventilation, air filtration, reducing crowding, wearing masks whenever indoors (even if not within 6 feet or 2 meters of others), attention to mask quality and fit, and higher-grade PPE for healthcare and other staff when working in contact with potentially infectious people.

Prevention of Outbreaks

Adenoviruses usually cause respiratory illnesses or conjunctivitis, and outbreaks can occur throughout the year and may spread more quickly in closed populations such as in hospitals, nurseries, day care facilities, schools, orphanages and swimming pools. There is no specific time of year when adenovirus infections and outbreaks are more common.

To prevent healthcare-associated outbreaks of adenovirus infections, health care providers should strictly follow infection control practices, including: contact and droplet precautions, environmental cleaning with appropriate disinfectants, prompt response and reporting of clusters of cases.

Sporadic cases and outbreaks of adenovirus have been reported of acute respiratory illness. Adenovirus type 14 which has been associated with outbreaks of acute respiratory illness among U.S. military recruits and the public. Severe outcomes have been recorded with Adenovirus types 4 and 7 particularly in people with weakened immune systems. In the last 10 years, instances of severe illness and death from adenovirus type 7 infection have been reported in the United States.

Outbreaks of Epidemic keratoconjunctivitis (Adenovirus types 8, 19, 37, 53, and 54,) and gastroenteritis (types 40 and 41), have also been reported usually in children.

Spread in bodies of water

Some adenoviruses (e.g., 4 and 7) that spread in bodies of water, such as small lakes or swimming pools without adequate chlorine and can cause outbreaks of febrile disease with conjunctivitis.

Outbreaks of adenovirus can be caused by new adenovirus variants with a high virulence for patients without immunodeficiency. Therefore, continuous monitoring of adenovirus infection is advised together with genetic analysis of viral strains over time to forecast the risk of outbreak in community. In contrast to most other respiratory viral infections adenovirus infections lead to long lasting immunity to reinfection to the same serotype.

VACCINATION

Currently, there is no adenovirus vaccine available for the public.

CONCLUSION

Adenovirus is a type of virus that most commonly causes upper and lower respiratory infections. It can also cause a variety of other illnesses, including gastrointestinal infection, neurological infection, and eye infection. Its outbreaks can occur throughout the year and may spread more quickly in closed populations. Disease is usually mild and self-limiting. Severe disease is a possibility in immunocompromised patients or those with existing respiratory or cardiac disease. Treatment is symptomatic and supportive. To prevent healthcare-associated outbreaks of adenovirus infections, health care providers should strictly follow infection control practices. Research in adenovirus infection has generally been limited relative to other respiratory disease viruses. Although, recombinant adenoviruses currently are used for a variety of purposes, including gene transfer in vitro, vaccination in vivo, and gene therapy. Several features of adenovirus biology have made such viruses the vectors of choice for certain of these applications.

....about CD Alert

CD Alert is a technical bulletin of the National Centre for Disease Control (NCDC), Directorate General of Health Services, to disseminate information on various aspects of communicable diseases to medical fraternity and health administrators. The bulletin may be reproduced, in part or whole, for educational purposes.

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