



## Adenovirus an Increasing Concern in West Bengal - Manifestation, Detection, Prevention and Treatment

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### Abstract

Human Adenovirus (hAdv) infections are currently at a surge in India with West Bengal holding a prominent place. Patient cohort with majority being children are getting reported with flue like symptoms, low oxygen level and upper respiratory tract infection. Diarrhoea and pink eyes are also getting noted. Clinical manifestations by different serotypes of the aforementioned DNA virus were previously confined to multifaceted mild symptoms but recently taking a serious toll mainly due to mutant varieties of the virus. Since contamination spreads mainly through droplet infection and faecal-oral route, personal hygiene holds most superior preventive measure. Patient infective swabs, stool and/or blood can be tested for presence of hAdv by different diagnostic methods, PCR based techniques being commonly followed in most pathological laboratories. Number of patients both paediatric and adults are getting admitted in different hospitals of West Bengal with increasing reports of hAdv infection. Treatments for specific clinical symptoms are provided to admitted cases, whereas certain drugs like Ganciclovir and Ribavirin are used to treat severe hAdv infections, but with variable success rate. Drug Cidofovir had shown some degree of moderate success in treatment of immune-compromised hAdv patients. However, no specific treatment has been reported till date for hAdv infection.

**Keywords:** Adenovirus; hAdv; Infection; Diagnosis; Reported Cases; West Bengal

### Abbreviations

hAdv: Human Adenovirus; ABP: Anandabazar Patrika; GI: Gastro Intestinal; ARDS: Acute Respiratory Distress Syndrome; PCR: Polymerase Chain Reaction; qPCR: Quantitative Polymerase Chain Reaction; LAMP: Loop-Mediated Iso-Thermal Amplification; PCR-ELISA: PCR-Enzyme Linked Immunosorbent Assay; ARI: Acute Respiratory Infection; NICED: National Institute of Cholera and Enteric Diseases; ICU: Intensive Care Unit; HDU: High Definition Unit; QMRA: Quantitative Microbial Risk Assessment

### Introduction

Adenoviruses are icosahedral, non-enveloped, ubiquitous DNA particles considered as etiologic agents for a wide spectrum of global pathogenesis including infections involving the upper or

lower respiratory tract, gastrointestinal (GI) tract, urinary tract or conjunctiva [1-3]. The outer surface structure and genetic makeup of the virus play critical roles in its pathogenicity. The outer surface fibers of the virus assist with its attachment and absorption into the host cell (Figure 1). Two common attachment receptors on the cell surface are

coxsackieadenovirus receptors (used by all subgroups except B) and membrane cofactor protein CD 46 (used by B except types 3 and 7). For most Adenovirus groups, coxsackie and CD46 are not used simultaneously. After interaction with host cell receptors, there is integrin-mediated endocytosis [4]. Clinical manifestations range from mild, self-limited disease to fatal dissemination [5,6]. A sudden surge in Human adenoviral (hAdv) infections as per

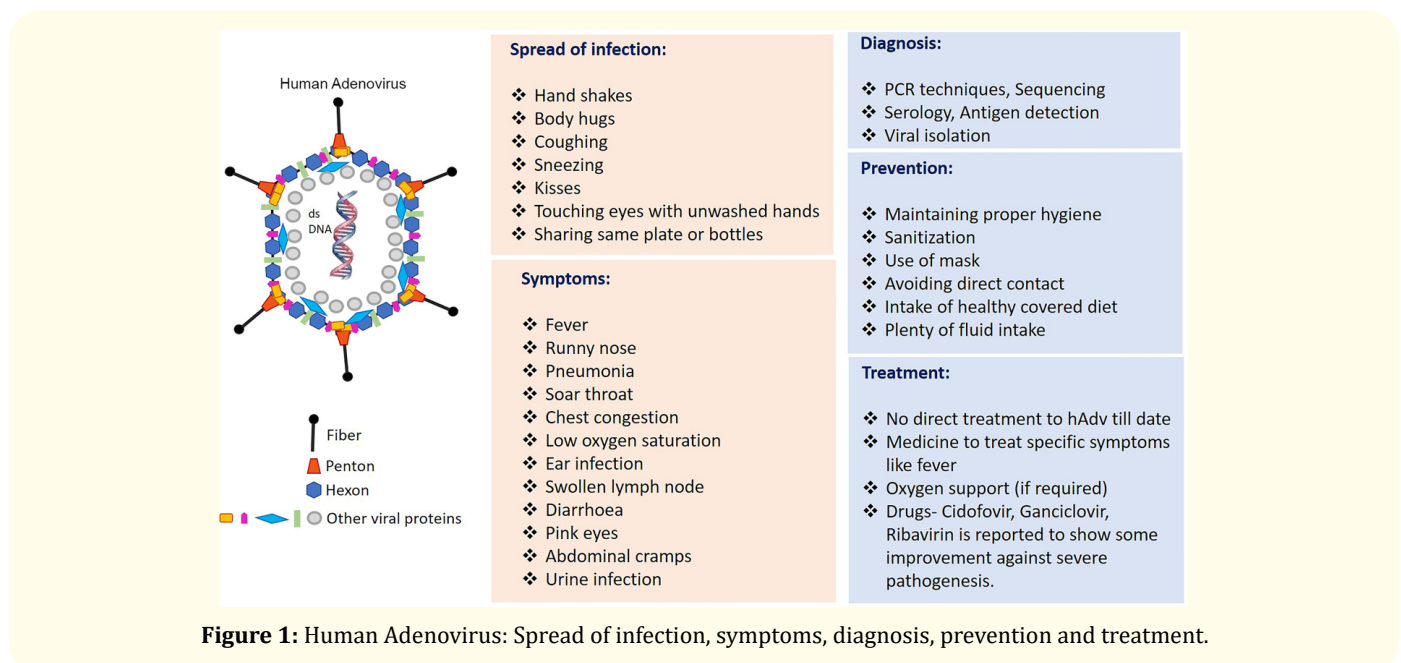
increasing daily case reports is posing a serious global threat. In the last few years, especially a large scale of Asian population, has suffered from adenoviral infections presented as acute respiratory distress syndrome (ARDS), while recently India being at a considerable risk. Though people of all age groups could be prone to infection, children and immune compromised patients are the most vulnerable cohort for hAdV attack [6-9]. About 1.76 million deaths occur due to gastroenteritis among children (aged < 5 years) globally, where involvement of hAdVs has been gaining prominence as stated in a reported of 2011 [3]. An acute severe hepatitis without any identifiable cause among young children (aged < 1 month to 16 years) was observed after the publication of disease outbreak news on 23 April 2022 by WHO. Otherwise considered an outcome of Covid-19, a considerable patient population were found to be hAdV positive as well [7,10]. New adenoviral strains are leading to thousands of hospitalizations in India while West Bengal alone contributing to a considerable disease load as per daily news updates. A deluge of child admission with respiratory tract infection is emanating an increasing concern.

**Adenovirus infection and diagnosis: A general overview**

Adenoviruses are classified into seven species or subgroups (A-G) with more than 50 serotypes [5,10-13]. Approximately one-third of the serotypes are associated with human disease. Different serotypes display different tissue tropisms that correlate with clinical manifestations of infection [13].

Symptoms can include fever, pneumonia, pharyngitis, tonsillitis, cough, sore throat, diarrhoea, vomiting, abdominal pain, keratoconjunctivitis. Viral transmission can occur through inhalation of aerosolized droplets, via faecal-oral route, direct conjunctival inoculation, exposure to infected tissue, blood

or environmental surfaces. The incubation period for hAdVs inside their host ranges from 2 to 14 days, depending upon viral serotype and transmission mechanism [1]. Nasopharyngeal swab, conjunctival swab, stool and sera are selective patient samples for detection of hAdV infection depending upon clinical manifestations of the disease [9,15,16]. Molecular practices are employed for hAdV diagnosis after presumptions based on clinical symptoms and syndromes [4]. Some common tests performed are Adenovirus-Polymerase Chain Reaction (PCR), antigen detection, serology, sequencing and viral isolation (Figure 1) [2,8,16,17]. PCR based methods are considered as most specific and affordable technique for viral detection. It is conceivable to detect Adenovirus by the former method using variability of clinical specimens, including throat swabs, nasopharyngeal lavage fluid, stool and blood samples [17]. Multitude of different PCR based approaches for detecting hAdV are inclusive of quantitative PCR (qPCR), general PCR, Loop-mediated iso-thermal amplification (LAMP), Multiplex PCR and PCR-enzyme linked immunosorbent assay (PCR-ELISA) to name most common methods [11,17]. Most PCR based diagnostic techniques follow a kit-based protocol. The underlying basics for all being amplification of a targeted DNA fragment (here viral DNA sequence) with known oligo primers using polymerization reaction. Different PCR techniques are generated by modification of the basic principle as per requirement. While qPCR enables detection and simultaneous quantification of the target, LAMP helps for a much-sophisticated detection and quantification of target DNA at a constant temperature thereby generating a characteristic fluorescence causing a change in turbidity. While multiplex PCR is designed to detect multiple hAdV types simultaneously, PCR-ELISA is fashioned to combine immunological techniques with the concept of PCR for diagnosis of Adenovirus [2,17,18]. On the



**Figure 1:** Human Adenovirus: Spread of infection, symptoms, diagnosis, prevention and treatment.

other hand, a PCR assay, applicable to clinical specimens, was developed that could detect all known serotypes of hAdvs with high sensitivity and allow for serotype determination by sequencing of the amplicons. Primers were designed from the conserved region of the viral hexon gene [19].

### Current scenario of West Bengal: Status of hAdv infection in 2023 as per local reports

- **Symptoms:** West Bengal presently is observing an unprecedented rise in the reported cases with flu like symptoms like low fever which escalates to high temperature (up to 102-103°F) and respiratory infections mainly in children. Other manifestations like infection in eyes, urinary tract, intestines, vomiting and diarrhoea are also getting noted [20-23]. Doctors' claims a probable susceptibility to lung fibrosis if respiratory symptoms persist about two months after infection [24].
- **Case Reports:** As per the reports generated by Dept. of Health Research (West Bengal), ABP published an article on February 19<sup>th</sup>, 2023 stating a total of 115 admitted cases on February 18<sup>th</sup> with respiratory issues in AMRI hospital (Kolkata), of which 22 patients (5 paediatric) were recruited in ICU/HDU. A rising hAdv positive diagnosis was observed in patients. The same report stated that an alarming increase in hAdv positive cases were observed since January 2023. Around 30 per cent of suspects' swab samples submitted to National Institute of Cholera and Enteric Diseases (NICED) for testing were found to be Adenovirus positive as declared by Dr. Shanta Dutta (Director, NICED) [22]. Another report published on 28<sup>th</sup> February, 2023 claimed a 50 per cent increase in infected cases compared to usual, West Bengal being in the grip of an unprecedented Adenovirus outbreak. Of the 500 samples tested by NICED from January-February 2023, 33 per cent were tested positive for hAdv [25]. On March 1, state's health secretary Narayan Swaroop Nigam visited different state-run hospitals in Kolkata after several deaths of children due to Adenovirus infection. According to the state government, 5,213 cases of Acute Respiratory Infection (ARI) were reported in the state in the previous one month [26]. As per IANS report, there had been claims of 48 deaths in just 11 days in the state. Whereas general secretary of the Association of Health Service Doctors, claimed out of 6-7 paediatric deaths, 30 per cent showed Adenovirus symptoms [23]. Yet another report

from the "The Guardian" stated that more than 12,000 cases of Adenovirus had been recorded in the state since January. More than 3,000 children had been admitted to hospital with severe flu-like symptoms. The Association of Health Service Doctors warned that the numbers of infected cases and deaths were much likely to be higher than the official statistics. Reports by local media had put the death toll at more than 100 children [21]. Co-morbidity and secondary infection are considered fatal towards disease severity and contagious nature of infection from children to parents. ABP report on 31<sup>st</sup> March, 2023 stated that 9 adult patients admitted to Apollo Multi-speciality Hospital had to be put to ventilation due to chest infection and were tested hAdv positive by comprehensive respiratory panelling as said by Dr. Debraj Jash. Admitted cases are more frequent in private hospitals than tertiary cares due to limited infrastructure of the latter [24].

- **Common hAdv infective strains:** Viral mutation could be an evolutionary advantage of the pathogen for better host invasion, survivability and evasion from host immune attack [27,28]. While previous studies have already reported hAdv type 7 (hAdv-7) invasion to be the main cause of upper respiratory tract infection, bronchitis and pneumonia in children [29], according to local reports, health officials claim several mutated hAdv strains being responsible for current severity of infection. Two mutants are identified as major contributors of infection risk with a new strain originating from the combination of serotype 3 and 7 causing havoc with at least 40 children dying in West Bengal alone. This strain is responsible for mass ICU admissions, with decreasing oxygen saturation and considered as most 'notorious' [30-33].

### Prevention and treatment for hAdv infection

Proper infection control and hygiene policies are best preventive measures against outbreaks and epidemics of adenoviral infections. Adenoviruses are spread by respiratory droplets or by the faecal-oral route. Therefore, patients admitted with suspected or confirmed Adenovirus infection should be maintained on droplet and contact precautions. The methodology of Quantitative Microbial Risk Assessment (QMRA) is also a preventive measure applied to drinking water and food for precaution against hAdv infection at the workplaces [34]. The treatment for Adenovirus respiratory tract infections primarily consists of supportive care

provided to patients. To date, there is no approved antiviral therapy in immunocompetent patients, especially because the illness is usually self-limited. Drinking plenty of fluid, taking general fever medicines and oxygen support (if required) may be general treatment strategy. Although there are many nucleoside analogues that will inhibit hAdV replication *in vitro*, few appear to work against the disease and infection *in vivo* [4,35]. Anecdotal reports exist of Ganciclovir and Ribavirin which are being used to treat severe adenoviral disease in immunocompromised individuals, but these drugs have shown variable success. Presently, Cidofovir is the only well identified and studied antiviral agent that has shown moderate success in adenoviral respiratory tract infections (Figure 1). It is commonly used in immunocompromised patients with acute infection [4,6]. Cidofovir is a cytosine monophosphonate analogue whose active metabolite, Cidofovir diphosphate, inhibits viral DNA polymerase. However, its use may be limited because of toxic events [35]. Vaccination against Adenovirus was approved only for U.S military against type 4 and 7 by the U.S. Food and Drug Administration on March 2011 [6,36].

## Conclusion

To summarise, Adenoviruses are DNA viruses classified into seven species or subgroups (A-G) with more than 50 serotypes. The outer surface fibers of the virus assist with its attachment and absorption into the cells. The risk of hAdV infection ranges from mild to severe manifestations inducing multifaceted symptoms. Children and immune-compromised adults are more prone to infection showing a contagious nature of the disease. Current case reports are at a surge in our country with West Bengal holding a prominent place. Most reported symptoms include upper respiratory tract infection, flu like symptom, fever, often complaint of diarrhoea. Patient swab, stool or blood are the common samples used for detection of the presence of virus as per the clinical manifestations. Various PCR based diagnosis are most common approaches, while techniques like sequencing and direct viral count can also be employed. A new viral strain originating from the combination of hAdV serotype 3 and 7 is found to cause maximum havoc. No prominent treatment strategy is yet established except general treatment for fever, oxygen support etc. Though different reports state certain drugs like Ganciclovir and Ribavirin are being used to treat severe adenoviral disease yet with a variable success rate. Cidofovir is the only recognized, well-studied antiviral agent that has shown some success in adenoviral respiratory tract

infections but has complicated side effects. Thus, personal hygiene, quality management, plenty of fluid intake and self-precaution remains best preventive measures to avoid infection.

## Conflict of Interests

The authors declare that there is no conflict of interest.

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