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REVIEW ARTICLE

Adenoviral Infections in Immunocompetent Children

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Abstract
Adenoviruses are a common cause of upper and lower respiratory infections, gastroenteritis and conjunctivitis in children. Although most adenoviral infections are self-limited, those caused by certain serotypes during outbreaks have led to severe pneumonias and poorer outcomes, with sequelae of bronchiectasis and bronchiolitis obliterans in survivors. Rarer manifestations such as central nervous system and urinary infections can also lead to severe disease. Adenoviruses can be shed for prolonged periods after infection and can also lead to persistent subclinical infection with the potential for reactivation during periods of immunosuppression. Diagnosis with polymerase chain reaction (PCR) testing is highly sensitive and specific but attributing causation in PCR positive children will depend on the presence of symptomatic disease. Treatment is predominantly supportive with maintenance of hydration in gastroenteritis and respiratory support in severe pneumonia. Although antiviral drugs are used in immunocompromised and transplanted children, they are not recommended for use in immune competent children especially in the absence of efficacy data. As adenoviruses are spread by droplet transmission and can survive on surfaces for weeks, infection control measures include isolation of patients, proper disinfection and use of personal protective equipment. Because adenoviruses are known to undergo spontaneous mutations and recombinant events leading to novel viruses and have caused fatal co-infections in the past, molecular surveillance of adenovirus is needed to monitor circulating serotypes, to recognise new disease emergence and to prevent epidemic spread.

Keywords Adenovirus infection · Epidemic serotypes · Severe pneumonia · Adenoviral gastroenteritis · Adenoviral conjunctivitis · Molecular adenoviral surveillance

Adenoviral Infections in Immunocompetent Children

Adenoviruses cause mostly self-limited upper and lower respiratory tract infections, gastroenteritis, conjunctivitis, genitourinary infections and rarely, neurological disease in both immune and immunocompromised children who acquire the infection through respiratory droplet or fecal-oral transmission. However, unprecedented recent outbreaks of acute adenoviral respiratory infections with increased hospital admissions for severe pneumonia and deaths among children in India have cast the spotlight on adenoviral serotypes with epidemic potential that can lead to severe disease and fatalities in normal children [1, 2].

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Etiology and Pathogenesis

Adenoviruses, first isolated from human adenoid tissue in 1953, are double-stranded DNA viruses that belong to the family Adenoviridae and are classified into genera based on their preferred hosts into those infecting mammals (*Mastadenovirus*, including human adenoviruses), birds (*Aviadenovirus*), cattle, reptiles, and amphibians (*Barthadenovirus*), fish (*Ictadenovirus*), other non-mammalian vertebrates (*Siadenovirus*) and tortoises (*Testadenovirus*) [3]. Human adenoviruses number over 110, subclassified based on serotype and genotype into 7 species labelled A to G, whose species-specific tissue tropism results in varying clinical manifestations after infection (Table 1) [4, 5].

Children acquire infection through respiratory droplets, fecal-oral transmission or contact with contaminated food, water or surfaces. Adenoviral entry into the cell triggers the innate immune response by activating natural killer (NK) cells, macrophages and pro-inflammatory cytokines and inducing memory cells, and the adaptive immune response

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Table 1 Human adenovirus species classification and clinical manifestations [4, 5]

Species	Important serotypes	Common sites of infection	Clinical manifestations	Type of spread
A	12, 18	Respiratory	URI, pneumonia	Endemic
	31	Gastrointestinal	Infantile gastroenteritis	Sporadic
B	3, 7, 14, 21, 55	Respiratory, conjunctiva	URI, pneumonia Pharyngoconjunctival fever	Epidemic and endemic
	11, 34, 35	Genitourinary	Hemorrhagic cystitis, interstitial nephritis	Sporadic
C	1, 2	Respiratory	URI, pneumonia	Endemic
	5	Hepatic	Hepatitis	Sporadic
D	8, 19, 37	Conjunctiva	Epidemic keratoconjunctivitis	Epidemic
E	4	Respiratory, conjunctiva	URI, pneumonia conjunctivitis	Epidemic and endemic
F	40, 41	Gastrointestinal	Infantile gastroenteritis	Endemic
G	52	Gastrointestinal	Infantile gastroenteritis	Sporadic

URI Upper respiratory infection

characterized by production of type-specific antibodies and antigen-specific CD4+and CD8+T-cells that cross-react with different adenoviral species. This robust immune response most often leads to clearance of adenoviral infection in 7–10 d in immunocompetent children. However, high levels of proinflammatory cytokines and chemokines including IL-1, -6, -8, -10, IFN-Ɣ and TNF have been known to cause increased disease severity especially in young children with no pre-existing immunity [5].

Following recovery from pneumonia, shedding of adenovirus from respiratory samples has been documented to last 51–97 d which is longer than the duration of shedding of other respiratory viruses such as respiratory syncytial virus (RSV; 4 d), rhinovirus (11 d) and influenza (18 d). Asymptomatic shedding of adenovirus could contribute to endemic circulation and epidemic outbreaks. Some adenoviral infections can lead to persistent subclinical infection in tonsillar and adenoidal tissue and lymphocytes of the gastrointestinal tract, that can later lead to viremia and reactivation of adenoviral infection during immunosuppression or following hematopoietic stem cell transplants. Finally, spontaneous mutations and recombinant events between two adenovirus serotypes infecting the same cell, as well as human and zoonotic (simian) interspecies recombinations have given rise to novel adenoviruses (B55 and E4) associated with outbreaks and the potential for global transmission [5–7].

Epidemiology

Adenoviral infections mainly occur among young children, with 80% diagnosed in children younger than 5 y of age [7–12]. Although adenoviruses can cause respiratory, gastrointestinal and conjunctival infections throughout the year with no well-defined seasonality in India [12, 13], the presence of seasonal peaks in other countries [7, 8, 13] may reflect differences in circulating adenovirus serotypes both between countries and within countries between seasons and between years [9, 14], assessment of which is often hampered by the absence of systematic molecular adenoviral surveillance. Adenoviral infections may be acquired sporadically or year-round with endemic serotypes such as 1, 2 and 5 [15], or during epidemics with serotypes 3 and 7 as reported from the US and Korea [8, 16] as well as from India in recent years [2, 12].

Adenovirus has been detected using polymerase chain reaction (PCR) in respiratory specimens from children with lower respiratory tract infections (LRTIs) at rates ranging from 3.7% in India [17] through 5.8% in China [9], 7.5-8% in the USA and Madagascar [10, 18] and 13.5% in India [2] to as high as 26% in South Africa [19]. In African countries, adenovirus is among the top three respiratory viruses identified from children with LRTI [20]. However, attributing a causal role to adenoviral infections in all LRTIs where they are identified is often problematic as adenoviruses are also identified at equally high rates from healthy individuals (Table 2) [21–26]. This finding is probably due to the ubiquitous nature of the virus with nearly all children infected by 6 y of age, the fact that several adenovirus species such as A and D cause mild or asymptomatic infection and that very few infections due to species C and F are seen in older children suggesting that they acquire protective immunity due to infections early in life [5, 14]. However, molecular surveillance studies have documented that infections with certain serotypes such as 7 and 3 from species B cause more severe disease compared to other serotypes [8, 9, 27], with adenovirus 7 associated with more severe clinical outcomes compared to serotype 3 due to its enhanced cytokine response and resulting severe airway inflammation [8]. Adenoviruses in LRTIs are often found as co-infections with other respiratory viruses where increased severity of infection has not been documented, whereas co-infection with *Streptococcus pneumoniae* has been associated with poorer outcomes [9, 28].

Adenoviral infections cause 2–15% of acute diarrhea in children. The incidence of adenoviral gastroenteritis also differs between various countries and locations. The serotypes most often implicated in adenoviral gastroenteritis are 40 and 41 from species F [4, 13, 29, 30]. Adenoviral diarrhea is more commonly seen in those younger than 2

Table 2 Disease attributable risk of common respiratory viruses in children with LRTI compared to controls [21–26]

Country, year	Case vs. control diagnosis, specimens, test	Viral etiologies (%) among cases (*N*)	Viral etiologies (%) among controls (*N*)	Odds ratios (95% CI) for viral etiology
Kenya, 2013 [21]	SARI < 5 y age vs. healthy controls Nasopharyngeal/ Oro-pharyngeal swabs, PCR	Cases 199	Controls 93	
		RSV 25%	RSV 8.6%	2.9 (1.3–6.7)
		Influenza A/B 11%	Influenza A/B 2.2%	4.8 (1.1–21)
		Adenovirus 22.6%	Adenovirus 18.3%	0.89 (0.5–1.8)
Kenya, 2015 [22]	SARI < 5 y age vs. healthy controls Nasopharyngeal/ Oro-pharyngeal swabs, PCR	Cases 731	Controls 115	
		RSV 21.2%	RSV 2.6%	10.15 (3.2–32.6)
		Influenza A/B 13.3%	Influenza A/B 5.2%	2.71 (1.2–6.4)
		Adenovirus 30.2%	Adenovirus 23.5%	1.51 (0.9–2.4)
South Africa, 2016 [23]	Pneumonia/ Severe disease vs. healthy/ URI + children. Nasopharyngeal swab/ Induced sputum, PCR	Cases 284	Controls 412	
		RSV 23%	RSV 4%	8.05 (4.2–15.4)
		Influenza A/B/C 11%	Influenza A/B/C 3%	4.13 (2.1–8.3)
		Adenovirus 19%	Adenovirus 10%	2.15 (1.3–3.5)
India, Madagascar, Mali, Paraguay, 2017 [24]	Hypoxemic pneumonia vs. non-hypoxemic pneumonia Nasal swab/ Aspirate, PCR	Cases 70	Controls 335	
		RSV 25.7%	RSV 13.1%	2.3 (1.2–4.3)
		Human metapneumovirus 14.3%	Human metapneumovirus 6.9%	2.3 (1.0–5.0)
		Adenovirus 5.7%	Adenovirus 7.8%	0.7 (0.2–2.1)
The Gambia, Kenya, South Africa, Mali, Thailand, Bangladesh, 2017 [25]	Radiological pneumonia vs. no pneumonia Naso-/ Oro-pharyngeal swabs, induced sputum, PCR	Cases 1166	Controls 398	
		RSV 24.8%	RSV 15.3%	2.08 (1.5–2.9)
		CMV 50.8%	CMV 52.2%	0.82 (0.64–1.1)
		Adenovirus 13.2%	Adenovirus 14.8%	0.72 (0.51–1.0)
Bangladesh, 2020 [26]	Severe acute malnutrition with pneumonia vs. those without pneumonia Nasopharyngeal wash, PCR	Cases 360	Controls 334	
		RSV 8.9%	RSV 0.9	13.1 (1.6–106.1)
		Influenza 4.5%	Influenza 0.6%	8.7 (1.0–78.9)
		Adenovirus 6.4%	Adenovirus 7.9%	1.4 (0.6–3.5)

CMV Cytomegalovirus; *LRTI* Lower respiratory tract infection; *PCR* Polymerase chain reaction; *RSV* Respiratory syncytial virus; *SARI* Severe acute respiratory infection; *URI* Upper respiratory infection

y of age [30] and second only to rotavirus as a causative organism of diarrhea among those 0–6 mo of age. Children with adenoviral diarrhea are less likely to be febrile than those with rotaviral diarrhea but more likely to have fever compared to those with diarrhea due to norovirus, sapovirus, or astrovirus. Exclusive breastfeeding has been shown to be strongly protective against adenoviral diarrhea [13]. Children with adenoviral gastroenteritis can also have respiratory symptoms [31], while children infected with the primarily respiratory serotypes 3 and 7 can also have acute abdominal pain, diarrhea and vomiting [8, 32].

Adenoviral infections are the commonest cause of conjunctivitis world-wide, and because of their ubiquitous nature and the fact that many of those affected do not seek medical attention, precise data on incidence is difficult to obtain. Epidemic keratoconjunctivitis is caused by the species D serotypes 8, 19 and 37 while pharyngoconjunctival fever, commonly due to serotype 3, has presented as outbreaks in schools and summer camps where the source of infection is often contaminated water reservoirs including swimming pools [4].

Clinical Manifestations

The commonest symptoms of adenoviral disease in children are fever, cough, coryza and breathlessness associated with *upper respiratory infections (URIs)*, that often go undetected and under-reported due to their mild and self-limited nature, and *lower respiratory tract infections (LRTIs)* of which pneumonia is the commonest. Other manifestations include pharyngitis, conjunctivitis, and diarrhea (Table 3) [8–10, 12, 33, 34]. The incubation period depends on the infecting serotype and can range from 2 d to 2 wk [4].

Respiratory Infection

Adenoviral pharyngitis is an acute self-limited illness that presents with fever, sore throat, exudative tonsillitis and

Table 3 Clinical manifestations of adenovirus infection in children, from various studies [8–10, 12, 33, 34]

Symptoms and signs of adenoviral infections	Findings in children from various studies, in percentages
Symptoms	
Fever	31–100%
Cough	60–99%
Breathlessness	27–66%
Wheezing	42–64%
Nasal discharge	16–43%
Sore throat	14–36%
Abdominal pain/ Vomiting	5–57%
Irritability	18–24%
Seizures	1–15%
Signs	
Pneumonia	14–85%
Croup	8–33%
Bronchiolitis	7–24%
Hepato/splenomegaly	34–52%
Diarrhea	5–43%
Tonsillar enlargement	29%
Conjunctivitis	5–24%
Lymphadenopathy	12%
HLH	5%
Sinusitis/ Otitis media	1%
Meningitis	1%
Kawasaki disease	1%

HLH Hemophagocytic lympho-histiocytosis

cervical lymphadenopathy, as well as nasal congestion in young infants. Adenovirus also causes *bronchiolitis* in infants similar to that caused by other viruses.

Pneumonia due to adenovirus is characterized by symptoms of influenza-like illness (ILI) or severe acute respiratory illness (SARI) similar to those caused by other respiratory viruses that are often more commonly associated with pneumonia than adenovirus [2]. While most adenoviral respiratory infections are self-limited, severe and fatal infections are often seen with epidemic spread of serotypes 7 and 3. In children with adenoviral pneumonia, need for oxygen supplementation and/or mechanical ventilation has ranged from 27% [10] to 46% [8]. Mortality in adenoviral pneumonia ranges from 5.5% [35] in surveillance studies to 12–13% [8, 33] in hospitalized children, and can be as high as 23–33% in children with severe adenoviral pneumonia [36–38]. Severe adenoviral pneumonia with its associated necrotizing inflammation of alveoli and bronchioles can lead to sequelae of bronchiectasis in 25% [39] and bronchiolitis obliterans in up to 36% of children [40], especially in those with duration of fever > 10 d, dyspnea or need for mechanical ventilation. Rarer extrapulmonary complications include myocarditis, meningitis, hepatitis, disseminated intravascular coagulopathy and hemophagocytic lymphohistiocytosis (HLH) [4, 33].

Eye Involvement

Adenoviral conjunctivitis can present as acute follicular conjunctivitis, epidemic keratoconjunctivitis or pharyngoconjunctival fever. *Acute follicular conjunctivitis* presents with itching, burning sensation, lacrimation, serous discharge and conjunctival congestion with follicular lesions on the palpebral conjunctiva. *Epidemic keratoconjunctivitis* is more severe with photophobia, conjunctival edema and membrane formation, corneal inflammation (keratitis) and preauricular adenopathy in addition to the above symptoms as well as high fever, vomiting and diarrhea in children under 2 y of age. In *pharyngoconjunctival fever*, however, photophobia and lacrimation are unusual, and children present with cough and sore throat with tonsillar enlargement and pharyngeal congestion with exudates similar to streptococcal pharyngitis. Examination of the eyes reveals granular palpebral conjunctiva with bulbar conjunctival hemorrhage. Symptoms usually resolve in 5–10 d [4, 41].

Gastrointestinal Infection

Adenoviral gastroenteritis has a clinical presentation similar to any other viral diarrhea in children, although some may have additional symptoms of conjunctivitis, rhinitis or pharyngitis. Although serotypes 40 and 41 are common causes of adenoviral diarrhea, infections with serotypes 3 and 7 have also been known to cause abdominal pain, vomiting and diarrhea. Adenoviral gastroenteritis is usually self-limited and resolves in 2–3 d. Children with gastroenteritis alone without respiratory symptoms tend to have shorter duration of fever of 1–2 d compared to those with respiratory symptoms who can be febrile for up to 5 d [11]. Rarer manifestations of adenoviral infection include mesenteric adenitis, appendicitis, intussusception and hepatitis [4].

Hepatitis: Hepatitis is an uncommon manifestation of adenoviral infection, occurring sporadically after serotype 5 infections. In 2022, cases of *severe acute hepatitis of unknown etiology* affecting a total of 3636 young children were reported from 35 countries, of whom 1.8% died and 6% needed a liver transplant. Although adenovirus serotype 41 was identified from peripheral blood in most children initially, it is a non-hepatotropic virus and was absent in liver biopsies in affected children. Adeno-associated virus 2 (AAV-2), a parvovirus that can only replicate in the presence of a helper virus such as adenovirus was found in liver cells and blood in cases but not controls, suggesting that AAV-2 co-infection with adenovirus 41 could have triggered an immune-mediated hepatitis. Waste-water surveillance

showed a correlation between numbers of hepatitis cases and the daily viral load of adenovirus and AAV-2 in wastewater, indicating community co-circulation of both pathogens during outbreaks. No similar cases of severe acute hepatitis have been reported after 2022 [42].

Genitourinary Infections

Acute hemorrhagic cystitis, usually caused by serotype 11, is an uncommon manifestation of adenoviral infection in boys and presents as acute onset dysuria and increased frequency of urine followed within 12–24 h by hematuria. Symptoms resolve within 2 wk and usually by 5 d of onset, without sequelae. Infants with severe pneumonia and disseminated adenoviral infection have occasionally been diagnosed to have *necrotizing tubulointerstitial nephritis* that can result in renal failure [4].

Central Nervous System (CNS) Manifestations

CNS manifestations of adenovirus infection, rare in immunocompetent children, include *febrile seizures*, *aseptic meningitis*, *acute encephalitis*, *acute demyelinating encephalomyelitis*, *and acute necrotizing encephalopathy*. Prodromal symptoms include fever with respiratory symptoms or diarrhea, with adenovirus isolated mostly from the respiratory or gastrointestinal tract but not from CSF. Outcomes are poor in over a-third, predictors of which include younger age, seizures, coagulopathy, absence of meningismus and isolation of serotype 2 [43].

Diagnosis

Molecular testing using PCR assays on nasopharyngeal swabs, bronchoalveolar lavage (BAL) specimens, stool, urine, tears or blood, based on the site of disease are standard for diagnosis of adenoviral infection. Real-time qualitative PCR testing has been shown to be ≥99% sensitive and specific for identification of adenovirus from respiratory specimens, blood, stool, urine and ocular swabs. However, as respiratory specimens or stool may be PCR positive due to viral shedding, interpretation of causation depends on the presence or absence of symptomatic adenoviral disease. Viral cell cultures and isolation are less subject to misinterpretation as adenovirus displays typical cytopathic effect on culture cells, but the lack of availability in many laboratories and the time taken for diagnosis make these impractical in most places. Other tests that may be used for diagnosis include adenovirus antigen tests or enzyme immunoassays on stool specimens in children with diarrhea, and direct fluorescent antibody and lateral flow immunochromatography testing on respiratory specimens, all of which are less frequently used than PCR testing [44].

Definitions to differentiate adenoviral infection and disease are useful because viral detection does not always implies disease, and co-pathogens may contribute to clinical symptoms. *Local infection* is defined as positive adenoviral PCR, antigen or virus isolation in a specimen other than peripheral blood, while *systemic infection* is defined as identification of adenovirus in a peripheral blood sample. *Probable disease* is defined as adenoviral infection with corresponding symptoms and signs without histological confirmation on biopsy, while *confirmed disease* is infection with symptoms and signs AND histological confirmation from the location of disease. Finally, *disseminated disease with multi-organ involvement* is defined as 2 or more PCR assays positive for adenovirus from peripheral blood and other sites, without other identifiable causes [44].

Other tests: C-reactive protein (CRP), procalcitonin, total WBC count, neutrophils and monocytes, IL-6, -8, -10 and IFN-Y are elevated in adenoviral infections but do not differentiate between adenoviral or bacterial infections [44]. Critically-ill children can have anemia, leukopenia, thrombocytopenia and elevated ferritin, lactate dehydrogenase (LDH), aspartate transaminase (AST) and D-dimer [38, 45]. Children with adenoviral gastroenteritis without respiratory involvement tend to have lower CRP values compared to those with respiratory manifestations [11].

Chest radiographs in adenoviral pneumonia commonly show peribronchial and perihilar infiltrates and atelectasis. Homogenous consolidation and pleural effusions that can be bilateral in up to two-thirds have been documented in children infected with serotypes 3 and 7. *Pleural fluid* analysis shows elevated protein and LDH and WBC counts (predominantly monocytes and neutrophils), elevated RBC counts in some and normal glucose [8, 10]. Findings on *computed tomography (CT)* of the thorax include bilateral and multifocal ground-glass opacities with associated patchy consolidation [46].

Treatment

As most adenoviral infections are self-limited, supportive care is often all that is necessary. This includes maintenance of hydration in acute gastroenteritis and provision of oxygen and respiratory support in severe pneumonia with oxygen therapy through high-flow nasal cannula (HFNC), non-invasive ventilation or mechanical ventilation [45].

The use of antiviral drugs to treat severe adenoviral pneumonia in non-immunocompromised children is controversial. Despite absence of efficacy data or controlled trials, Cidofovir has been used in children with adenoviral disease

after bone marrow transplantation with some evidence of benefit [47], as also documented in a few case reports of immune competent children with severe adenovirus manifestations [8, 48–50] and one case series of children with adenovirus-associated acute liver cell failure in 2022 [51]. It is administered at doses of 5 mg/kg every 1 to 2 wk or 1 mg/kg thrice weekly until resolution of viremia, with concomitant Probenecid and intravenous hydration to minimize nephrotoxicity. An orally available lipid conjugate of Cidofovir with reduced nephrotoxicity, Brincidofovir, has been used to prevent adenovirus disease in hematopoietic stem cell transplanted children [45].

No guidelines exist for Cidofovir or Brincidofovir use in non-immunocompromised children, nor for other modalities of treatment such as IVIG, monoclonal antibodies or donor-derived virus-specific T-cell therapy that have been used in transplanted children [45]. Intravenous immunoglobulin (IVIG) has been used at doses ranging from 0.8 g/kg single dose [50] to 1 g/kg daily for 2 d [52], with evidence of benefit when started before progression to severe adenoviral pneumonia in one study [52] but no evidence of benefit in another [53]. Steroids have been used in severe adenoviral pneumonia for their anti-inflammatory actions and benefit in children with acute respiratory distress syndrome (ARDS) [9, 37], but evidence of specific benefit against adenovirus infections is lacking [49, 53].

Prevention

Adenoviruses are resistant to intermediate-level disinfectants including alcohol and chlorhexidine and can survive for weeks on surfaces, thereby posing long-term infection risks. Proper infection control practices include isolation of patients, sanitizing surfaces with appropriate disinfectants including formaldehyde or bleach solutions for surfaces and steam autoclaving of instruments. Individual control measures to prevent transmission include good hand hygiene for at least 20 s with soap and water or hand sanitizer if soap is not readily available, contact and droplet precautions by using personal protective equipment with surgical masks and gloves when caring for patients, staying at home when ill and respiratory etiquette by covering the nose and mouth when sneezing or coughing [2]. The success of infection control precautions is evidenced by the almost complete disappearance of epidemic species B serotypes 3 and 7 in Beijing during the COVID-19 pandemic when public health measures to prevent COVID-19 transmission were in place [54].

Live attenuated oral vaccine against adenovirus serotypes 4 and 7 is available only for the US military and not recommended for those below 17 y of age. As vaccine virus can be shed in stool for 28 d, personal hygiene is recommended for military recipients especially if they are in contact with young children or those who are immunosuppressed [55].

Conclusions

Adenoviral disease is often unrecognised and under-reported due to its varied clinical manifestations. Although a large proportion of adenoviral illness is self-limited, the presence of serotypes that cause severe disease in young children and the absence of specific therapy against the virus contribute to the burden that this infection adds to global public health. In addition, the potential for recombinant events leading to novel viruses as well as potentially fatal co-infections make molecular surveillance of adenovirus essential to monitor circulating serotypes, to recognise new disease emergence and to prevent epidemic spread.

Declarations

Manuscript Guarantor Dr. Mona Basker, Head, Pediatrics Unit-III, CMC Vellore.

Conflict of Interest None.

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