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Adenoviral Respiratory Infection-Associated Mortality in Children: A Retrospective Case Series

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Abstract

Viral respiratory infections are a leading cause of illness and hospitalization in young children worldwide. Case fatality rates in pediatric patients with adenoviral lower respiratory tract infection requiring intensive care unit (ICU) admission have been reported between 7 and 22%. We investigated the demographics and clinical characteristics in pediatric mortalities associated with adenoviral respiratory infection at 12 academic children's hospitals in the United States. There were 107 mortality cases included in our study, 73% of which had a chronic medical condition. The most common chronic medical condition was immunocompromised state in 37 cases (35%). The incidences of pediatric acute respiratory distress syndrome (78%) and multiple organ dysfunction syndrome (94%) were profound. Immunocompetent cases were more likely to receive mechanical ventilation within the first hour of ICU admission

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(60 vs. 14%, $p < 0.001$) and extracorporeal membrane oxygenation (27 vs. 5%, $p = 0.009$), and less likely to receive continuous renal replacement therapy (20 vs. 49%, $p = 0.002$) or have renal dysfunction (54 vs. 78%, $p = 0.014$) as compared with immunocompromised cases. Immunocompromised cases were more likely to have bacteremia (57 vs. 16%, $p < 0.001$) and adenoviremia (51 vs. 17%, $p < 0.001$) and be treated with antiviral medications (81 vs. 26%, $p < 0.001$). We observed a high burden of nonrespiratory organ system dysfunction in a cohort of pediatric case fatalities with adenoviral respiratory infection. The majority of cases had a chronic medical condition associated with an increased risk of complications from viral respiratory illness, most notably immunocompromised state. Important treatment differences were noted between immunocompromised and immunocompetent cases.

Introduction

Viral respiratory infections are a leading cause of illness and hospitalization in young children worldwide.[1] Adenoviral respiratory tract infections occur primarily in infants and young children and can manifest as bronchiolitis, exacerbations of wheezing and asthma, croup, and pneumonia and pneumonitis in transplant recipients.[2,3] A significantly higher incidence of adenovirus infections has been observed in immunocompromised children.[4] In infants and children with adenoviral respiratory tract infection requiring admission to an intensive care unit (ICU), rates of respiratory failure and acute respiratory distress syndrome are high.[3,5–8]

Case fatality rates in pediatric patients with adenoviral lower respiratory tract infection requiring ICU admission have been reported between 7 and 22%.[3,5,6,9] In immunocompromised children with adenoviral respiratory infection requiring ICU admission, reported case fatality is greater than 50%.[7] In this study, we sought to investigate the demographics and clinical characteristics in a multicenter cohort of pediatric case fatalities associated with adenoviral respiratory infection.

Methods

We performed a multicenter retrospective cohort study identifying children less than 18 years of age with laboratory-confirmed adenoviral respiratory infection and in-hospital mortality between January 1, 2004, and March 31, 2019. The capabilities for case identification were institution-dependent, primarily based on the timing of conversion to electronic health records during the period of study, and thus most institutions were reliably able to identify cases for the 2009 to 2019 timeframe. The Institutional Review Boards at each of the participating sites reviewed the study protocol and each approved the study or deemed it nonhuman subject research.

Infection was defined as the identification of adenovirus from a nasopharyngeal or endotracheal specimen by polymerase chain reaction testing, immunochromatography, direct fluorescent antibody, hemadsorption, tube viral culture, or shell vial culture. We defined hospital-acquired adenoviral infection as positive specimens obtained after the first 48 hours of hospital admission.[8] We defined viral respiratory codetection as the identification of a different viral agent from a nasopharyngeal or endotracheal specimen using the aforementioned testing methodologies. Bacterial and fungal respiratory co-detection were defined as the identification of a bacterial or fungal pathogen in culture from: (1) an endotracheal specimen, (2) thoracentesis specimen, (3) bronchoalveolar lavage specimen, or (4) lung tissue specimen at autopsy.

Review of the patient chart and clinical and administrative databases was conducted to collect case characteristics and clinical data. We identified cases with chronic medical conditions associated with an increased risk of complications from viral respiratory illness.[10,11] These conditions included the following: (1) chronic pulmonary conditions such as asthma, cystic fibrosis, restrictive lung disease, or chronic lung disease as diagnosed by a pediatric pulmonologist (e.g., supplemental O_2 and/or pharmacological therapies); (2) unrepaired or palliated cyanotic heart disease; (3) prematurity, defined as gestational age < 32 weeks and chronological age < 12 months; (4) pregnancy; (5) immunocompromised state such as solid organ or hematopoietic stem cell transplantation, neutropenia, or human immunodeficiency virus; (6) neuromuscular disorders such as muscular dystrophy, motor neuron disease (e.g., spinal muscular atrophy), and cerebral palsy; and (7) hemoglobinopathy. The diagnosis of pediatric acute respiratory distress syndrome was established using the Pediatric Acute Lung Injury Consensus Conference definition.[12] The International Pediatric Sepsis Consensus Conference criteria for organ dysfunction was used to establish a diagnosis of multiple organ dysfunction syndrome (MODS).[13] The Pediatric Index of Mortality-3 was calculated for each case at the time of admission to the ICU to establish a severity of illness index and corresponding predicted probability of death.[14] We performed stratified analyses on case immune system status (immunocompromised vs. immunocompetent) to assess for differences in clinical characteristics and therapies provided.

Individual site data were entered into a REDCap electronic case report form hosted on a secure server located at the University of Virginia School of Medicine. Continuous variables were assessed for normality using Shapiro–Wilk testing and were compared using Student's *t*-test or Wilcoxon rank sum

testing as appropriate. Categorical variables were compared using Chi-square or Fisher's Exact testing as appropriate. Type I error was set at 0.05. All calculations were performed using Stata/IC 12.1 (Stata Corporation, College Station, TX).

Results

There were 107 mortality cases from 12 institutions included in our study. The median age of cases at time of adenovirus diagnosis was 35 months (interquartile range [IQR], 9–81 months) and 73% of cases had a chronic medical condition associated with an increased risk of complications from viral respiratory illness.[10,11] The most common chronic medical condition was immunocompromised state in 37 cases (35%) with the following etiologies: hematopoietic stem cell transplant (HSCT) recipient (24 cases), neutropenia (7 cases), solid organ transplant (2 cases), severe combined immunodeficiency (2 cases), and medication-induced (2 cases). Forty-one percent of cases had hospital-acquired adenoviral disease. Demographic and clinical characteristics of the cases are presented in ►**Table 1**. There was no clear seasonal trend noted based on the month of first positive viral test (►**Fig. 1**).

We compared clinical characteristics and therapies received based on immune system status (►**Table 2**). Immunocompetent cases were more likely to receive mechanical ventilation within the first hour of ICU admission (60 vs. 14%, $p < 0.001$) and have community-acquired adenoviral disease (80 vs. 19%, $p < 0.001$). The median time from hospital admission to acquisition of first positive adenoviral test was 12 hours (IQR, 0 hours to 2 days) in immunocompetent cases and 39 days (IQR, 7–72 days) in immunocompromised cases. Immunocompetent cases were more likely to receive invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO; $p = 0.04$ and $p = 0.009$, respectively) as compared with immunocompromised cases. In total, only nine cases (six immunocompromised, three immunocompetent) did not undergo invasive mechanical ventilation and all had advanced directives precluding intubation. There were no differences in the rates of utilization of inhaled nitric oxide or high-frequency oscillatory ventilation between the groups.

The incidence of MODS was very high and observed in 94% of the cases. The median number of organ dysfunctions was four (IQR, 2–5) in immunocompetent cases and five (IQR, 4–6) in immunocompromised cases ($p = 0.002$). There were no differences in the rates of respiratory, cardiovascular, or neurological dysfunctions between immunocompetent and immunocompromised cases. Immunocompromised cases were more likely to have renal, hepatic, and hematological dysfunctions as compared with immunocompetent cases ($p = 0.014$, $p = 0.001$, $p < 0.001$, respectively). In the setting of increased renal dysfunction, immunocompromised cases were more likely to receive continuous renal replacement therapy (CRRT; $p = 0.002$) as compared with immunocompromised cases.

Detection of an additional respiratory viral agent occurred in 42 (39%) cases with human rhino/enterovirus (27 cases) being the most common agent recovered. Bacteria from a respiratory specimen was recovered in 44 (41%) cases with *Pseudomonas aeruginosa* (21 cases) being the most common. Six cases (6%) had recovery of fungi from respiratory specimens with *Aspergillus fumigatus* (3 cases) being the most common. Growth of bacteria or fungi in culture from a sterile blood specimen occurred in 32 (30%) and 5 (5%) cases, respectively. Adenovirus was detected by polymerase chain reaction testing in the blood of 31 cases (29%), 19 of which were immunocompromised. There were no differences in the rates of respiratory pathogen co-detection based on immune status though immunocompromised cases were more likely to have bacteremia (57 vs. 16%) and adenoviremia (51 vs. 17%; for both, $p < 0.001$).

Immunocompromised cases were more likely to be treated with antiviral medications ($p < 0.001$). All 48 cases who received antiviral therapy received cidofovir. Additionally, four cases (two immunocompromised) received brincidofovir and two cases (both immunocompromised) received ribavirin in addition to cidofovir. Two immunocompromised cases received cytotoxic T lymphocytes directed at

Table 1 Demographic and clinical characteristics

Characteristic	Number (%) or median (IQR): ($n = 107$)
Age (months)	35 (IQR, 9–81)
Hospital-acquired infection	44 (41%)
Chronic medical conditions[a]	78 (73%)
Immunocompromised state	37 (35%)
Chronic pulmonary condition	26 (24%)
Neuromuscular disease	20 (19%)
Prematurity	12 (11%)
Cyanotic congenital heart disease	7 (7%)
Hemoglobinopathy	0
Pregnancy	0
PIM-3% ROM	1.8 (IQR, 0.8–15)
Hospital LOS (d)	20 (IQR, 8–63)
ICU LOS (d)	14 (IQR, 5–25)
pARDS	83 (78%)
Organ dysfunction	
Respiratory	107 (100%)
Cardiovascular	91 (85%)
Neurological	73 (68%)
Hematologic	56 (52%)
Renal	67 (63%)
Hepatic	55 (51%)
MODS	101 (94%)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MODS, multiple organ dysfunction syndrome; pARDS, pediatric acute respiratory distress syndrome; PIM, Pediatric Index of Mortality; ROM, risk of mortality.

[a]Eighteen cases with two or more chronic medical conditions associated with an increased risk of complications from viral respiratory illness.

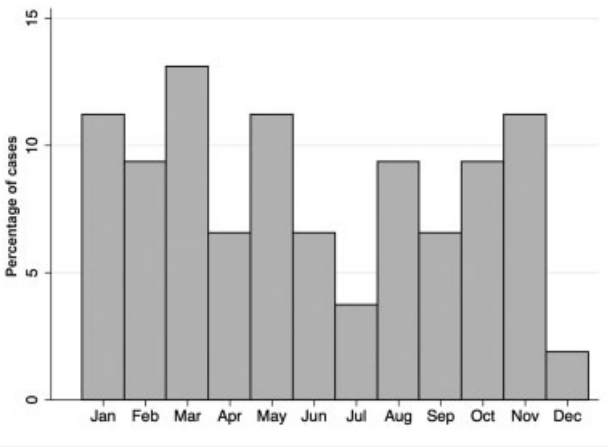

Fig. 1 Distribution of cases based on month of first positive viral test.

adenovirus. Antiviral use was high among the cohort of HSCT cases (92%). Of the non-HSCT cases, 50% of those receiving antiviral medications had adenoviremia. Among the cases that received antiviral medications, the incidence of both renal dysfunction (81 vs. 48%) and CRRT utilization (50 vs. 14%) were increased (for both, $p < 0.001$). Overall, 30% of patients received systemic corticosteroids for a pulmonary indication and was more common in immunocompromised cases (43 vs. 23%, $p = 0.03$).

We further stratified the 37 immunocompromised case fatalities into HSCT (24 cases) and non-HSCT (13 cases) groups. HSCT cases were more likely to have received antiviral therapy with cidofovir (92 vs. 62%, $p = 0.04$) though there were no differences in the rates of adenoviremia between the groups (50 vs. 54%). We observed no other differences in terms of demographics, method of adenoviral acquisition, severity of illness, organ dysfunctions, therapies received, or co-detection of other infectious agents between HSCT cases and non-HSCT immunocompromised cases.

Discussion

In a cohort of pediatric case fatalities with adenoviral respiratory infection, we observed a high burden of nonrespiratory organ system dysfunction. The majority of cases had a chronic medical condition associated with an increased risk of complications from viral respiratory illness, most notably immunocompromised state. Immunocompromised cases were more likely to have hospital-acquired adenoviral disease. Important treatment differences were noted between immunocompromised and immunocompetent cases.

Table 2 Comparison of clinical characteristics and therapies received based on immune system status

Characteristic	Immunocompromised state no. (%) or median (IQR): ($n = 37$)	Immunocompetent state no. (%) or median (IQR): ($n = 70$)	*p*-Value
Age (months)	69 (IQR, 25–130)	24 (IQR, 6–52)	<0.001
HA infection	30 (81%)	14 (20%)	<0.001
PIM-3% ROM	0.9 (IQR, 0.8–1.4)	5.5 (IQR, 1–36)	<0.001
Hospital LOS (d)	67 (IQR, 31–128)	11 (IQR, 5–24)	<0.001
ICU LOS (d)	20 (IQR, 10–33)	10 (IQR, 4–22)	0.004
pARDS	29 (78%)	54 (77%)	0.88
MODS	37 (100%)	64 (91%)	0.09
Organ dysfunction			
Respiratory	37 (100%)	71 (100%)	1.0
Cardiovascular	33 (89%)	58 (83%)	0.57
Neurological	25 (68%)	48 (69%)	0.92
Hematologic	33 (89%)	23 (33%)	<0.001
Renal	29 (78%)	38 (54%)	0.014
Hepatic	27 (72%)	28 (41%)	0.001
IPPV	31 (84%)	67 (96%)	0.04
HFOV	16 (43%)	27 (39%)	0.64
ECMO	2 (5%)	19 (27%)	0.009
Inhaled nitric oxide	16 (43%)	25 (36%)	0.45
CRRT	18 (49%)	14 (20%)	0.002
Antiviral medication	30 (81%)	18 (26%)	<0.001
Steroids	16 (43%)	16 (23%)	0.03

Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HA, hospital-acquired; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; IQR, interquartile range; LOS, length of stay; MODS, multiple organ dysfunction syndrome; pARDS, pediatric acute respiratory distress syndrome; PIM, Pediatric Index of Mortality; ROM, risk of mortality.

From an epidemiological standpoint, among children with viral respiratory infection requiring admission to the ICU, adenovirus demonstrates a lower incidence of detection, but higher case fatality, than respiratory syncytial virus, human rhino/enteroviruses, and influenza.[3,5,6,8,9,15–20] In our cohort, we observed that nearly all cases had dysfunction of more than one organ system. While there is limited data in pediatric nonsurvivors of viral respiratory infection, our observation suggests a higher incidence of MODS in adenovirus case fatalities as compared with human rhino/enteroviruses, influenza, and human metapneumovirus.[20–22]

Adenovirus displays broad tissue tropism with several different organ systems at risk, though severe illness is most often seen with respiratory infection and disseminated disease.[4,23] Cell-damaging effects of adenoviral infection and the host immune response are responsible for the observed tissue pathology and clinical manifestations.[4] In fatal cases of pediatric adenoviral disease, elevated levels of interleukin-6, interleukin-8, and tumor necrosis factor-α have been observed, which may help explain the high incidence of cardiovascular dysfunction and shock state in our cohort.[24,25]

There is currently no approved antiviral treatment for adenovirus in North America or Europe though cidofovir is routinely used as a preemptive therapy in HSCT patients and we noted widespread use among our immunocompromised cases.[26] It was notable that 25% of immunocompetent cases received cidofovir despite a relatively low rate of adenoviremia in this group. Nephrotoxicity from cidofovir is an important concern and can be worsened with the concomitant administration of some common antimicrobial and immunosuppressive medications.[26] We noted a higher incidence of renal dysfunction and CRRT utilization in the cohort of cases receiving cidofovir.

We observed some distinct differences in clinical presentation and resource utilization based on immune system status. Immunocompromised cases, the majority of which had undergone HSCT, had longer inpatient lengths of stay prior to, and were less sick at the time of, admission to the ICU. In HSCT patients, the most common time for adenoviral infection is 2 to 3 months post-transplantation, which is congruent with our findings.[23] Immunocompetent cases were more likely to be admitted directly to the ICU, have a higher severity of illness on ICU admission, and were more likely to receive ECMO. Pediatric ECMO survival for adenoviral respiratory infection has hovered around 50% for the past 25 years, though survival for immunocompromised children is substantially worse at 36%.[27] Until recently, immunocompromised state was considered a relative contraindication for the use of ECMO, which may inform our finding of decreased use in that group. Finally, our observation that immunocompromised cases were less likely to undergo invasive mechanical ventilation is the result of these cases being more likely to have an advanced directive that precluded intubation.

There are several limitations to this study, most notably the retrospective nature and inability to investigate the epidemiology of adenovirus by subtype in our cohort. Furthermore, as a result of the transition to electronic health records at all of the participating institutions over the last two decades, the timeframe over which each institution could reliably identify cases was variable. As such, we presumably missed several eligible cases in the early part of our search range (i.e., ~2004–2009). A strength of our study is the inclusion of cases from a variety of academic pediatric institutions with a broad geographic distribution—all with the availability of ECMO and half with active HSCT programs.

In pediatric case fatalities associated with adenoviral respiratory infection, we observed a profound degree of nonrespiratory system organ dysfunction, far greater than seen in published studies of other common respiratory viruses. A significant proportion of case fatalities are immunocompromised children who are more likely to have hospital acquisition of adenoviral disease. Important clinical differences were noted between immunocompromised and immunocompetent cases and require further study.

Conflict of Interest
None declared.

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