Adenovirus Respiratory Infection among Immunocompetent Patients in a Pediatric Intensive Care Unit During 10-year period: Co-morbidity is common

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ABSTRACT: **Background:** Adenovirus is responsible for 2–7% of childhood viral respiratory infections, 5–11% of viral pneumonia and bronchiolitis. Most are self-limited but may cause severe respiratory infection.

Objectives: To describe adenovirus respiratory infection in immunocompetent children in a pediatric intensive care unit (PICU).

Methods: Children with adenovirus respiratory infection in our PICU from 2007 to 2016 were included. Data were retrospectively retrieved, including background, clinical manifestation, and treatment. Adenovirus was diagnosed by polymerase chain reaction, immune fluorescence, or both.

Results: Of 9397 samples, 956 were positive for adenovirus in children hospitalized during the study period. In total, 49 patients (aged 2 months–11.5 years) were admitted to our PICU, five were immunocompromised and excluded from the study, 19/44 (43%) were referred from other hospitals. Twenty-eight (64%) had underlying conditions, 66% had fever and cough, 11% had conjunctivitis, and 34% received antibiotics before admission. White blood cell counts ranged from 790 to 34,300 (mean 14,600) and 36% had counts above 15,000. Chest X-ray was consistent with viral infection in 77% of patients and normal in three (13.6%). Viral co-infection was found in 9 patients, 7 had presumed bacterial super-infection, and 27 (61.4%) needed mechanical ventilation. Two patients received cidofovir, 33 (75%) steroids, and 37 (84%) antibiotics. Four patients died.

Conclusions: Adenovirus respiratory infection may cause severe disease necessitating PICU admission and mechanical ventilation, mostly in patients with underlying conditions. Many patients received steroids and antibiotics, which may be unnecessary. Mortality was 9%, mainly among young infants and those with underlying conditions.

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KEY WORDS: adenovirus, immunocompetent, pediatric, pediatric intensive care unit (PICU), respiratory infection

Human adenoviruses are a group of at least 68 non-enveloped viruses containing double-stranded linear DNA. They are classified into seven species (A–G) according to their biophysical, biochemical, and genetic characteristics [1,2]. Adenovirus plays a significant role in pediatric infections, accounting for 2–7% of respiratory illnesses overall and 4–20% of the pneumonias [2-4]. A correlation between specific types and different syndromes has been reported, as well as a correlation between severe forms of adenovirus and specific serotypes (i.e., 3, 7, and 23) [2,5-7]. Most infections are self-limited or present with mild respiratory symptoms, but some patients can become severely ill with a need for intensive care, which includes high rates of morbidity and even mortality [8-10]. Patients who are prone to severe illness are those with an altered immune system or neonates, but there are severe cases reported in immunocompetent patients. Those reports describe adults and adolescents, mainly during outbreaks, with sparse data regarding the pediatric population [11,12]. Cidofovir has emerged as the preferred antiviral agent for adenovirus, although no randomized controlled trials have confirmed the benefit, and there are many case reports and uncontrolled case series to support treatment, mainly in immunocompromised and severely ill patients [2,13].

In a previous study, adenovirus was detected in 2% of children ≤ 2 years of age with bronchiolitis hospitalized at our center, mostly in combination with other pathogens [14]. Most data and case reports present immunocompromised patients or outbreaks in adults or pediatric patients in long-term facility care or in the army [5,8,12,15,16]. The aim of our study was to describe the epidemiology of immunocompetent pediatric patients hospitalized with adenovirus respiratory infection in our pediatric intensive care unit (PICU).

PATIENTS AND METHODS

This retrospective study included all patients with laboratory-confirmed adenovirus respiratory infection who were admitted to our PICU, from 2007 to 2016. Our hospital is a tertiary pediatric center that serves the northern area of Israel (about 1 million citizens). Polymerase chain reaction (PCR), immune fluorescence

(IFA), or both were used to diagnose adenovirus. Real time PCR became the uniform method for diagnosis in 2010. Analytical sensitivity of the real time PCR respiratory test for adenoviruses in the laboratory is 8 copies/reaction (200 copies/ml) (data from the Quality Control for Molecular Diagnostics tests).

The analytical specificity is high. We do not have cross-reactivity with other respiratory viruses diagnosed in the laboratory (influenza A and B, parainfluenza, adenovirus, hMPV, RSV [respiratory syncytial virus]), as well as herpes viruses (HSV-1, HSV-2, CMV, EBV, VZV, HHV-6), BK virus, and enteroviruses.

Cultures are not a routine test in our hospital. There is a reference laboratory in central Israel that can examine the serotype, but this is not routine. Positive cases were counted if the clinical presentation was consistent with viral infection and the results were positive for adenovirus. Secondary bacterial infection was defined as the isolation of bacteria in blood, or in the cases of pneumonia: lobar consolidation, high fever, leukocytosis, and inflammatory markers.

Data collection included demographic and background information on the patients, clinical presentation, co-infection, treatment in the PICU (ventilator support, antibiotic and antiviral treatment), and outcome.

The study was approved by the local institutional review board.

RESULTS

During the study period, 9397 samples were taken for adenovirus (1444 during the years 2007–2010 and 7953 during the years 2010–2016) from all departments in the pediatric hospital. The increase in the number of tests is probably related to the method, the easily availability of tests, and the awareness of the physicians. Of these, 956 (10%) were positive for adenovirus. During the years 2007–2010, 3% were positive, and during the years 2010–2016, 11% were positive. Our PICU sent 707 samples. Adenovirus was positive in 49 patients (five were immunocompromised). Forty-four immunocompetent patients were admitted to the PICU, 19 referred from other hospitals [Table 1]. Age range was 2 months to 11.5 years (mean 2.15 years). Most patients (40 children) were younger than 5 years of age, 30 patients were older than 2 years old. Underlying conditions were found in 28/44 (64%): 8 patients had congenital heart disease, 13 patients had respiratory diseases (3 were born prematurely and had bronchopulmonary dysplasia, 3 had upper airway obstruction, 3 had severe hyper-reactive airway disease, 4 had severe chronic lung disease, 2 of them had respiratory ventilation at home, 5 had neurological co-morbidity (mainly retardation and convulsions), and 2 had metabolic disease. Mean duration of symptoms before admission was 2.9 days. Of these, 29/44 (66%) had fever and cough, 5/44 (11%) had conjunctivitis, and 15/44 (34%) received antibiotics before admission [Table 2]. White blood cell counts (WBC) on admission ranged from 790–34,300 cells/ml^3 (mean 14,600). Blood samples were taken between 0 and 7 days from presentation (mean 2.875 days).

Table 1. Patients (n=44) characteristics and risk factors

Parameter	Number (%)
Male	29 (66)
Age range, years	0.08–10
Mean age, years	2.15
Median age, years	1.16
Patients < 5 years	40 (90)
Mean length of symptoms before hospitalization	2.9 days
Mean ± SD PICU hospitalization days	9.16 ± 9.75
Median PICU hospitalization days	6
Mean ± SD hospitalization days	15.4 ± 12.2
Median hospitalization days	10
Any co-morbidity	28 (64)
Cardio-respiratory (% from any co-morbidity)	21 (75)
Neurologic (% from any co-morbidity)	5 (18)
Metabolic (% from any co-morbidity)	2 (7)

PICU = pediatric intensive care unit, SD = standard deviation

Table 2. Clinical characteristics of patients with adenovirus respiratory infection

Parameter	Number (%)
Cough	29 (66)
Fever	29 (66)
Conjunctivitis	5 (11)
Diarrhea	6 (14)
Antibiotic treatment before hospitalization	15 (34)
Mean WBC (cells/mm^3)	14600
Normal WBC (5000–15,000)	24 (55)
Viral co-infection	9 (20)
X-ray typical for viral infection	34 (77)
Bacterial co-infection	7 (16)
Pneumonia	4 (9)
Group A streptococcus severe infection	2 (4.5)
Mastoiditis	1 (2)
Ventilation	27 (61)
Mean ventilation, days	8.8
Median ventilation, days	5
Antibiotic treatment	37 (84)
Treatment with cidofovir	2 (4.5)
Intravenous immunoglobulin	5 (11)
Corticosteroids	33 (75)
Inhalations	32 (73)
Overall mortality	4 (9)

WBC = white blood cells

In 16 patients (36%), WBC was above 15,000 and in 3 patients (7%) WBC was < 5000 cells/ml^3. These low blood counts were recorded on days 2 or 3 of the disease.

Chest X-ray was consistent with viral infection in 34/44 (77%), and normal in six (13.6%) patients. Mechanical ventila-

tion was needed in 27 (61.4%) patients for a mean duration of 8.8 days (range 1–36 days, median 5 days).

Viral co-infection was found in nine patients (7 RSV, 1 parainfluenza, 1 human metapneumovirus).

Seven patients were diagnosed with secondary bacterial infection: four had pneumonia, one had mastoiditis (*Fusobacterium necroforum*), 2 had group A *Streptococcus* invasive infection (one with fulminant sepsis and one with peritonitis).

Two patients received cidofovir. One patient was a 5-year-old male with severe psychomotor retardation who received the drug before he was transferred to our hospital and did not receive the drug at our hospital. The other patient was a 6-month-old male, previously normal with severe acute respiratory distress syndrome and myocarditis with both adenovirus and RSV positive respiratory infection. Since he was very ill and immunodeficiency was not ruled out at the moment, he received intravenous immunoglobulin and cidofovir. Both patients survived. Of the immunocompetent patients 33/44 (75%) received steroids and 37/44 (84%) received antibiotics.

Four (9%) patients died within 30 days of adenovirus detection. All were younger than 18 months. Three had underlying conditions. One patient, without any apparent co-morbidity, was a 10-month-old previously healthy male infant who presented with fulminant group A streptococcal (GAS) sepsis after a few days of upper respiratory tract infection. PCR for adenovirus and human metapneumovirus (HmPV) was positive in his respiratory samples. Two other patients, both with congenital heart disease, presented after partial surgical correction. One, a 6-month-old boy, was discharged home but returned after a few days with adenovirus and heart failure; he died the next day. The other, a 7-month-old female with hypoplastic left heart disease, was hospitalized in the PICU for one month and died with heart failure and pneumothorax. Adenovirus was positive in her respiratory secretion. The fourth patient, a 1.5-year-old female with chronic pulmonary disease and developmental delay, presented with respiratory syndrome. Two days later, she was admitted to our PICU and died 3 days following admission of respiratory failure. No autopsy was performed on any of these patients.

DISCUSSION

Adenovirus is a frequent cause of pediatric upper respiratory tract infections. Severe course with high morbidity and mortality was mainly described in immunocompromised patients (1,2,8,9,13). Hospital and nursery home care outbreaks have been described [15-17]. In the current study we focused on the immunocompetent pediatric population, not as part of an outbreak. Twenty-five of the patients admitted to our hospital were admitted to the PICU, and another 19 were referred from other hospitals. More than 60% of the PICU patients had underlying conditions. In a study over 17 years in Korea [10] in children, 4% (9/239) of episodes occurring in previously healthy children resulted in severe outcomes, while 31.3% (51/163) of children with underlying conditions presented with severe adenovirus infection. The Korean study included immunocompromised patients; 5/22 fatal cases were immunocompromised, eight had no risk factors and nine had other risk factors. Another description of an outbreak of adenovirus type 3 among long-term care facility patients in 2005 described 35 patients who were identified; 50% required PICU and two patients died [15].

In this study, most of the patients were younger than 5 years of age and almost 70% were below the age of 3 years. Moreover, the four patients who died were all younger than 18 months. In the study from Korea by Lee et al. [10], all of the patients who died with no underlying condition were younger than 2.5 years of age, except one who was 3.1 years old. All those with underlying conditions but without immunodeficiency were younger than 4.5 years. In another study, which described disseminated adenovirus in Texas [8], three patients had no underlying conditions and were 3, 11, and 21 months old, and another premature infant was 7 months old.

Secondary bacterial infection is a known complication of viral respiratory infections, including RSV, as well as adenovirus and other viruses [3,4,6]. In our cohort, seven (15%) patients had bacterial infection, four were diagnosed with pneumonia (typical for bacterial origin), two with invasive group A streptococcus and one with mastoiditis caused by *Fusobacterium necroforum*. This potential complication is sometimes hard to distinguish, since high fever, leukopenia or leukocytosis and even high C-reactive protein may accompany adenovirus infection [4]. This finding can also explain the common use of antibiotics in children with adenovirus respiratory infections. Young children who are ill-appearing are usually given antibiotic treatment, often unnecessarily. In a study published more than a decade ago, adenovirus was associated with many admissions and antibiotic use that was changed when the results returned [4]. In a PICU, the patients are more ill and fragile, but antibiotic treatment should be used with caution. However, careful attention should be given to young infants with severe adenoviral infection since they carry a risk for bacterial super infection. Treatment with cidofovir is an unresolved issue, mainly due to lack of controlled studies and the potential toxicity of the drug. Two of our patients received cidofovir (one before transfer to our hospital), and both survived. Treatment with cidofovir is well-documented in immunocompromised patients [13,18,19]. Treating immunocompetent patients has been sporadically reported, especially during outbreaks or among severe adult cases [16,17]. An animal model of a Syrian immunocompetent hamster study concluded that cidofovir (as well as chlorpromazine) could be useful in replication-associated cases [20]. Unfortunately, no double-blind studies demonstrated the advantage of its use. When describing an outbreak of adenovirus type 7, Ghanaiem and colleagues [16] treated two patients who survived, but did not treat another one because of renal failure, yet he also survived. The main side effect

of cidofovir is nephrotoxicity, and careful attention should be paid to those patients taking the medication [21,22]. Until more data regarding treating immunocompetent patients is available, treatment may be considered in severe cases, especially when immunodefiency has not been ruled out.

Mortality in immunocompetent patients was described mainly in the setup of outbreaks with (0–50%) described by Ghanaiem et al. [16]. A study in Argentina described the histopathology results of 18 children, mean age 8.25 months, who died due to adenovirus lower respiratory tract infection [23]. Bacterial super infection was diagnosed in 11/18, and the pathology was no different between the serotypes. Recently, another study showed a complicated course with multiple viral respiratory co-pathogens [24], and in another recent publication from Taiwan during one year records, only 5 patients out of 531 needed intensive care unit, all of whom recovered [25]. In our cohort, most of the co-infections were associated with RSV. It was not possible to compare among subgroups. In the patients who died, only the one with invasive GAS infections had adenovirus and HmPV.

Our study has some limitations due to its retrospective nature. The reason for antibiotic treatment for patients who were referred from other hospitals was not always documented. This single-center study was conducted at a tertiary center, which serves a population of 1 million people. Unfortunately, serotype or subgroups of adenovirus were not determined, and the relation between clinical syndrome severities and the subgroup was not possible to determine. A previous study from Israel reported respiratory serotypes in the years 2006–2008 [6]. The most prevalent serotypes of adenovirus were one (22.8%), two (19.2%), seven (18%), and three (14%). Serotype C was more common in immunocompetent as compared to immunocompromised patients. In that study, 2/106 hospitalized patients were cared for in intensive care units, and one patient died.

CONCLUSIONS

Adenovirus is a common respiratory pathogen. It may cause severe disease necessitating PICU admission and mechanical ventilation, mostly in young children with underlying conditions. Steroids and antibiotics are commonly used. Four patients in our study died, all within 3 days of diagnosis associated with underling conditions or rarely due to secondary sepsis. More data regarding the function of the immune system of patients who are considered immunocompetent with acute severe viral infection are still needed. Careful attention to young children with cardiac or neurological conditions who are infected with adenovirus infection is warranted. Cidofovir may be considered in severe cases of laboratory-confirmed adenovirus infection.

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