Outbreak of Adenovirus Genome Type 7d2 Infection in a Pediatric Chronic-Care Facility and Tertiary-Care Hospital


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An outbreak of adenovirus infection that involved residents of a pediatric chronic-care facility, staff of a tertiary-care hospital, and a nosocomial hospital case was studied. In the pediatric facility, 31 (33%) of 93 residents had adenovirus infection, and 8 died. Risk factors for illness were an age of <7 years (P = .004), presence of a tracheostomy (P = .015), and residence on a particular floor (P < .001). In the tertiary-care hospital, 36 health care workers had adenovirus infection; 26 (72%) had failed to follow strict contact and droplet precautions, and 30 (83%) continued to care for patients while they had symptoms. A 5-month-old patient with underlying lung disease acquired severe adenovirus infection in this hospital. All isolates were adenovirus type 7 (Ad7). DNA restriction analysis revealed the band patterns of all isolates to be identical and characteristic of the genome type d2. Thus, Ad7d2 caused significant morbidity and mortality in persons in the pediatric chronic-care facility and tertiary-care hospital. This is the first published description of Ad7d2 strains in the United States.

Human adenoviruses cause infections that range in severity from mild or inapparent clinical syndromes to severe, life-threatening disease. There are at least 49 recognized serotypes; some are more highly pathogenic than others [1]. Adenovirus type 7 (Ad7) is a particularly pathogenic serotype that causes acute respiratory disease syndrome, pharyngoconjunctival fever, pneumonia, and CNS disease [1–6]. Infections commonly occur in children, and acute infection may lead to long-term respiratory sequelae, including bronchiectasis and hyperlucent lung or McLeod syndrome [7–10]. Persons at particularly high risk for disseminated or life-threatening Ad7 infection include those who are immunocompromised or those who have underlying lung or cardiac disease [11–14]. Ad7 was the third most common serotype reported to the World Health Organization from 1967 through 1976, following types 1 and 2 [15]. Ad7 infections occur sporadically or in outbreaks, depending on the epidemiological setting, underlying herd immunity, and, possibly, virus strain [6]. Outbreaks generally occur in settings that have close living conditions, such as military barracks, hospital wards, and chronic-care facilities [11–13, 16–19]. Outbreaks of Ad7 infection have been reported in neonatology and general pediatric units [12, 13, 19] and in pediatric chronic-care facilities, which are at increased risk for both adenovirus spread and significant morbidity and mortality secondary to underlying disease [11, 17, 18]. A recent report of the emergence of Ad7 in Japan illustrates the epidemic potential of this virus over broad geographic regions [20]. During 1981–1992, reports of Ad7 infection numbered...
1–4 per year and constituted <1% of total adenovirus isolates within Japan, whereas in the years 1995, 1996, and 1997, the number of isolations of Ad7 increased to 104, 220, and 234, respectively, and Ad7 caused more severe illness than did other adenovirus serotypes. In the United States, outbreaks of Ad7 infection were more commonly associated with military recruits, until routine use of the live adenovirus types 4 and 7 vaccines dramatically reduced adenovirus-associated morbidity in this population [21, 22]. Civilian outbreaks of Ad7 infection have not been as frequently reported in the United States, possibly because of the lack of readily available laboratory resources that are necessary to confirm a diagnosis. The full impact of Ad7 on hospitals and chronic-care facilities is likely to be underestimated.

To understand better the geographic and temporal distribution of Ad7 strains and the potential for correlation with virulence factors, enzyme restriction fragment analysis has been used to classify Ad7 into at least 27 genome types [23–39]. Both globally dispersed and geographically restricted genome types of Ad7 have been identified by use of this method, and shifts or replacements of predominant genome types over time have been documented. In Europe and Australia, Ad7c was replaced by Ad7b in 1969 and 1974, respectively, and Ad7e was replaced by Ad7b in 1982 in Brazil [26, 28, 34, 39]. In Argentina, Uruguay, and Chile, a shift from Ad7c to Ad7d was shown in 1986 [25]. In China, Ad7d replaced Ad7b as the predominant strain in the 1980s [37]. Recently, a new genotypic variant, designated Ad7i, was described in an 8-month-old boy in Argentina; the infection resulted in a fatal outcome [40]. The former Soviet Union and Israel have reported unique genomic types indigenous to their respective countries [30, 38]. It is unclear whether there are correlations between the genetic variability of Ad7 and the degree of severity of associated illness.

Currently, few laboratories in the United States routinely type or further characterize adenovirus isolates. Of the few studies of Ad7 genomic variants in the United States, Ad7b was identified as the predominant genome type circulating from the early 1970s through the mid-1980s [12, 27, 28], the same genome type that was also responsible for outbreaks in Europe and elsewhere [6, 26, 41]. We describe an outbreak of Ad7 infection, genome type d2, that began in September 1998 in a Chicago pediatric chronic-care facility and then spread to a tertiary-care hospital. To our knowledge, this is the first outbreak of infection with adenovirus type 7d2 reported in the United States.

METHODS

Background and epidemiological investigation. Patient charts at the pediatric chronic-care facility from 1 September through 15 November 1998 were reviewed. Ninety-three residents were at the facility during the outbreak: 44 resided on the first floor and 49 on the second floor. Physical examinations of the residents were done primarily by 1 staff pediatrician or, rarely, by a substitute colleague. Residents at the facility were severely compromised neurologically; none were ambulatory. Forty-nine of the residents attended special schools. Younger and more severely impaired residents were placed on the second floor. Individual rooms housed 4 or 5 residents. The baseline mortality rate in the facility was ~0–2 deaths per month. Case definition for adenovirus infection was fever (temperature, ≥37.2°C) with respiratory symptoms (different from baseline) and/or conjunctivitis in the absence of another documented diagnosis.

The majority of ill residents from the pediatric chronic-care facility were hospitalized at hospital A. The infection control team at hospital A did an epidemiological investigation from 28 October through 15 December 1998. Health care workers (HCWs) were instructed to report to the employee health service if they became ill with symptoms compatible with adenovirus infection. A standardized questionnaire that contained questions pertaining to severity of illness and infection control practices was administered to HCWs. The case definition for adenovirus infection in the HCWs was conjunctivitis or ≥2 respiratory symptoms.

Specimen collection. From 28 October 1998 (time of outbreak recognition) through 16 November 1998, nasopharyngeal specimens for virus isolation were obtained from all residents of the pediatric chronic-care facility who met criteria for the case definition for adenovirus infection. Before 28 October, ill residents of the facility had respiratory viral cultures done as part of other diagnostic workups. All samples for culture were obtained within 1 week after onset of symptoms, except for 1 patient, whose samples were obtained 16 days after onset of symptoms. Nasopharyngeal, oropharyngeal, and/or eye specimens were obtained from hospital A HCWs who fit the case definition for adenovirus infection.

Laboratory investigation. Respiratory and eye specimens were inoculated into MRC-5 and A549 cells and were monitored for cytopathic effect. Adenovirus isolates were identified by use of commercial immunofluorescence assays and were typed by a microneutralization assay with type-specific reference equine antisera [42, 43]. An Ad7d2 prototype strain was kindly provided by Dr. Ella Mendelson (Central Virology Laboratory, Chaim Sheba Medical Center, Tel-Hashomer, Israel) for comparative purposes.

For genome typing by means of enzyme restriction analysis, purified adenovirus DNA was prepared by a modification of the method of Deryckere and Burgert [44]. Aliquots of ~1 μg of purified DNA were added to the appropriate restriction buffer that contained 10 U of restriction enzyme (BamHI, BglII, Smal, Hpal, HindIII BglII, BstEII, and BclI) in a total reaction volume of 40 μL and were incubated under conditions specified.
RESULTS

Pediatric chronic-care facility. At the time of the outbreak, the pediatric chronic-care facility housed 93 residents, who were segregated between floors according to age, size, and the level of complexity of care required. Younger, smaller, and more debilitated children were located on the second floor (n = 49; mean age, 8.0 years; median age, 6.4 years). The first floor housed residents who required less medical care (n = 44; mean age, 15.0 years; median age, 13.9 years). Of the 93 children, 31 (33%) fit the case definition for adenovirus infection. Of these 31, 11 (35%) were culture positive for adenovirus. On the second floor, 26 children (53%) fit the case definition, and 12 others (24%) met only 1 of the criteria for the case definition (temperature, ≥37.2°C, conjunctivitis, or respiratory changes). On the first floor, 5 children (11%) fit the case definition, and 7 others (16%) had only 1 sign. Adenovirus isolates were obtained from 10 children on the second floor and from 1 on the first floor (some residents did not have culture for viruses performed if illness occurred before the time of outbreak recognition).

Risk factors for illness were identified as age of <7 years, presence of a tracheostomy, and residence on the second floor (table 1). Floor of residence may have been significant because of multiple factors, including younger age, increased severity of underlying illness, and higher virus load. Eight (26%) of the 31 children who met the case definition died during this time period: 7 on the second floor and 1 on the first floor. All 8 children had fever and symptoms of worsening respiratory distress, which included increasing oxygen requirement, retractions, and change in secretions. Of these 8 fatal cases, 5 (63%) were culture-positive for adenovirus.

The index patient, a long-term resident, had onset of symptoms on 21 September 1998 and was the first resident to develop compatible illness (figure 1). The last case patient exhibited onset of symptoms on 30 October. The first positive adenovirus culture result was for a child who had onset of symptoms on 9 October. The last positive adenovirus culture result was for the last recognized case. Anecdotal information revealed that some staff and family members of residents had been ill in October with clinical symptoms that were compatible with adenovirus infection.

Hospital A HCWs. One tertiary-care hospital (hospital A) provided the majority of care to children from the pediatric chronic-care facility. Children who were admitted to hospital A were occasionally visited by staff from the facility and family members. On 28 October, it was apparent that several HCWs exhibited symptoms consistent with adenovirus infection (figure 1). A total of 42 HCWs were evaluated at the employee health service; 36 fit the case definition for adenovirus infection. The HCWs who met the case definition were registered nurses (56%), respiratory therapists (17%), clerks and aides (16%), and physicians (11%). The 36 employees were furloughed for 1–14 days, according to their respective duration of symptoms. Five HCWs (14%) were culture positive for adenovirus, which was isolated from a specimen from a respiratory site or the eye (table 2). However, culturing techniques were found to be highly variable among the staff in the employee health service, and thus the

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of residents</th>
<th>With adenovirus infection</th>
<th>P*</th>
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<tr>
<td></td>
<td>Total (n = 93)</td>
<td>With adenovirus infection (n = 31)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (57)</td>
<td>20 (38)</td>
<td>.302</td>
</tr>
<tr>
<td>Female</td>
<td>40 (43)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>29 (31)</td>
<td>15 (52)</td>
<td>.004</td>
</tr>
<tr>
<td>7–13</td>
<td>37 (40)</td>
<td>12 (32)</td>
<td>.111</td>
</tr>
<tr>
<td>14–32</td>
<td>27 (29)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>8 (9)</td>
<td>6 (75)</td>
<td>.015</td>
</tr>
<tr>
<td>Absent</td>
<td>85 (91)</td>
<td>25 (29)</td>
<td></td>
</tr>
<tr>
<td>Attends school</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>49 (53)</td>
<td>13 (27)</td>
<td>.144</td>
</tr>
<tr>
<td>No</td>
<td>44 (47)</td>
<td>18 (41)</td>
<td></td>
</tr>
<tr>
<td>Floor of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>49 (53)</td>
<td>26 (53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First</td>
<td>44 (47)</td>
<td>5 (11)</td>
<td></td>
</tr>
</tbody>
</table>

* Bivariate analysis.

P value was determined by use of 2-tailed Fisher’s exact test (all other P values were determined by use of Mantel-Haenszel χ² test).
number of adenovirus-positive cultures may have been an underestimation. A reported temperature of >38.3°C was associated with a positive culture result for adenovirus ($P = .02$; Fisher’s exact test). Of the 36 HCWs who fit the case definition, 30 (83%) had contact with a patient who was infected with adenovirus. Failure to adhere to strict contact and droplet precautions was noted in 26 HCWs (72%). Three (13%) of 24 HCWs reported consistently using face shields and masks when performing tracheostomy care. Thirty (83%) of the 36 HCWs performed patient care while they had symptoms. All 5 of the culture-positive HCWs reported working while symptomatic.

**Nosocomial case.** A 5-month-old patient with underlying bronchomalacia and teardrop trachea was admitted to hospital A at the end of October 1998 with the clinical and laboratory diagnosis of respiratory syncytial virus and reactive airway disease (figure 1). Initially, the course of hospitalization was unremarkable, and the patient improved. However, at the time of discharge (9 days after presentation), the patient was noted to have a temperature of 40°C and marked respiratory distress that quickly necessitated intubation and blood pressure support. An endotracheal viral culture revealed adenovirus. The hospital stay was lengthened by 1 month, and significant respiratory sequelae developed.

**Laboratory detection.** Seventeen adenovirus isolates (11 from pediatric chronic-care facility residents, 5 from HCWs at hospital A, and 1 from the patient with nosocomial infection at hospital A) were submitted to the Centers for Disease Control and Prevention (Atlanta) for typing. All isolates were identified as serotype 7 by type-specific neutralization. To further characterize the isolates, DNA restriction analysis was done [37, 38]. Representative DNA restriction patterns of adenovirus isolates from 1 pediatric chronic-care facility resident, 1 hospital employee, and the 1 patient with nosocomial infection are shown in figure 2. The restriction band patterns were identical for all of the isolates from this outbreak, and they matched patterns previously described for a novel genome type, designated “Ad7d2” [38]; the banding patterns were confirmed by means of parallel restriction analysis of an outbreak isolate with a known Ad7d2 strain from Israel (data not shown).

**DISCUSSION**

This outbreak illustrates the potential morbidity, mortality, and cost that can result from the introduction of Ad7 into a closed living community, such as a pediatric chronic-care facility, where adenoviruses can spread rapidly through respiratory secretions by direct person-to-person transmission and,

**Table 2. Characteristics of hospital A health care workers (HCWs) who fit the case definition for adenovirus infection ($n = 36$).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of HCWs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive adenovirus culture result</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Contact with adenovirus culture-positive patient</td>
<td>30 (83)</td>
</tr>
<tr>
<td>Failed to practice strict contact and droplet precautions</td>
<td>26 (72)</td>
</tr>
<tr>
<td>Performed tracheostomy care</td>
<td>24 (67)</td>
</tr>
<tr>
<td>Used face shields (of 24 total)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Remained on job while symptomatic</td>
<td>30 (83)</td>
</tr>
</tbody>
</table>

**Figure 1.** Cases of adenovirus infection, according to week of onset in 1998. Cases were identified according to clinical criteria for pediatric chronic-care facility residents, hospital A employees, and a patient with nosocomial infection. Hexagons denote case patients who were culture positive for adenovirus. Three hospital A employees did not have information available for determination of date of onset of clinical symptoms.
possibly, by fomites. Susceptibility to adenovirus infection is greater in younger individuals than in older individuals, because protective antibodies are lacking in younger patients [45]; thus, pediatric hospitals are at increased risk for the occurrence of outbreaks.

Additional infection control measures were instituted at both the pediatric chronic-care facility and hospital A. Contact and droplet precautions, along with more intensive hand washing recommendations, were emphasized to the staff. Although these infection control measures exist as routine policy at both institutions, staff surveys at hospital A revealed that consistent compliance with contact and droplet precautions did not occur. The initial suspected diagnosis of respiratory syncytial virus infection in these children led to the institution of contact precautions only, so many staff members did not use masks for close patient contact. In addition, frequent changes in staff within large facilities and the increasing demands on health care professionals within a patient care environment may have influenced strict compliance with multiple isolation precautions. Furthermore, both the chronic-care facility and hospital A instituted a strict policy of restricting ill employees. Of interest, anecdotal information from the pediatric facility, as well as the survey results from hospital A, indicated that many employees continued to work while they were ill. Reasons included loyalty to patients and colleagues, financial reimbursement, lack of realization of the diagnosis, and the complex scheduling of work shifts. Many of the employees stated that they did not feel sick enough to justify an absence from work. These infection control issues illustrate the difficulty in managing adenovirus outbreaks.

The circulation of Ad7d2 has not been previously documented in the United States, and outbreaks caused by Ad7d2 have not been described. Furthermore, Ad7d2 has only recently been identified in Israel, and strains most closely related to this variant, 7d and 7d1, have been previously identified only in China and Japan [37–39, 46]. Because the most recent adenovirus genome type data available from the United States are >10 years old, we were unable to determine when Ad7d2 emerged in this country and whether it was introduced from an outside source or evolved from an indigenous strain [27–29, 39].

Although there is no evidence that the emergence of Ad7d variants elsewhere in the world resulted in an increased incidence or severity of disease, certain Ad7 genome types may be associated with more severe clinical outcomes. In Argentina, Uruguay, and Chile, a novel genome type, Ad7h, has been linked to increased morbidity and mortality in infants [5, 47]. For example, in Argentina, 16 of 29 immunocompetent infants with acute lower respiratory disease caused by Ad7h were found to have required intensive care [5]. Community-wide outbreaks of acute lower respiratory tract infection of infants with Ad7h who required hospitalization occurred as recently as 1998 in Chile (A. Kajon, personal communication). Recently, Ad7h strains have been isolated in Japan [48]. Ad7h has not been documented in the United States. The predominant genome type identified in the United States from the early 1970s to the mid-1980s was Ad7b, a ubiquitous strain that had been identified worldwide [27–29]. Ad7b has caused most of the reported multiple outbreaks of respiratory illness in the United States [6, 12, 28]. Although the outbreaks were examples of severe disease in crowded pediatric facilities, the severity of Ad7 disease in the United States does not appear to equal the magnitude of outbreaks of disease in other areas of the world.

Estimates of the impact of Ad7 disease in the United States have been hampered by a lack of widely available resources for the typing of isolates. Although adenoviruses are isolated on many occasions when influenza or respiratory syncytial virus is suspected, complete identification is rare, because few laboratories perform serotyping and even fewer perform genomic characterizations. Moreover, many clinicians do not obtain specimens for viral culture when adenovirus is suspected because of the lack of effective antiviral therapy. Therefore, an
accurate estimate of the frequency of Ad7 infections and the composition and distribution of adenovirus genome types in the United States has not been possible.

Although the lack of antiviral therapy has made investigation of adenovirus infections a somewhat lower priority than other treatable respiratory virus infections, an effective oral vaccine that prevented outbreaks of Ad7 infection has been used by the military since 1971 [45, 49, 50]. In the late 1960s, adenovirus types 4 and 7 were shown to have been the cause of the majority of cases of acute respiratory disease syndrome in hospitalized basic military trainees [16]. Further studies demonstrated the oral adenovirus types 4 and 7 vaccines to be safe, immunogenic, and effective [51, 52]. From 1984 through 1994, no outbreaks of acute respiratory disease were attributed to adenovirus types 4 or 7 among military recruits who received the vaccines [53]. Vaccine production slowed in 1994 and ceased in 1996. Recently, the military performed a seroprevalence survey to assess the susceptibility of new US Army trainees to infection with adenovirus types 4 and 7 [45]. Results showed that 66% and 73% of trainees lacked antibodies to serotypes 4 and 7, respectively. Younger age and lack of previous military service were associated with susceptibility to infection. From May through December 1997, an outbreak of Ad4 infection occurred at a large army basic training center after vaccination of trainees was suspended [54]. The military experience illustrates the utility of these live adenovirus vaccines in closed community settings and raises the possibility of future outbreaks of infection caused by Ad4 and Ad7 within military barracks because of the current lack of available vaccines.

Ad7 infection is potentially preventable through vaccination. A recent study has shown no significant differences in neutralization among some Ad7 genome types, which implies that the Ad7 vaccine would likely protect against many of these different Ad7 variants [55]. Surveillance of adenovirus serotypes, along with molecular testing of Ad7 genomes by use of either nucleotide sequencing or restriction digest, are necessary to assess current and future disease caused by Ad7. The results of increased surveillance efforts should allow for identification of populations at risk for serious effects of Ad7 infection and determination of potential candidates to receive an Ad7 vaccine.

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References


