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Genotype Prevalence and Risk Factors for Severe Clinical Adenovirus Infection, United States 2004-2006

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Abstract

Background—Recently, epidemiological and clinical data have revealed important changes with regard to clinical adenovirus infection, including alterations in antigenic presentation, geographical distribution, and virulence of the virus.

Methods—In an effort to better understand the epidemiology of clinical adenovirus infection in the United States, we adopted a new molecular adenovirus typing technique to study clinical adenovirus isolates collected from 22 medical facilities over a 25-month period during 2004-2006. A hexon gene sequence typing method was used to characterize 2237 clinical adenovirus-positive specimens, comparing their sequences with those of the 51 currently recognized prototype human adenovirus strains. In a blinded comparison, this method performed well and was much faster than the classic serologic typing method.

Results—Among civilians, the most prevalent adenovirus types were types 3 (prevalence, 34.6%), 2 (24.3%), 1 (17.7%), and 5 (5.3%). Among military trainees, the most prevalent types were types 4 (prevalence, 92.8%), 3 (2.6%), and 21 (2.4%).

Conclusions—For both populations, we observed a statistically significant increasing trend of adenovirus type 21 detection over time. Among adenovirus isolates recovered from specimens from civilians, 50% were associated with hospitalization, 19.6% with a chronic disease condition, 11% with a bone marrow or solid organ transplantation, 7.4% with intensive care unit stay, and 4.2% with a cancer diagnosis. Multivariable risk factor modeling for adenovirus disease severity found that age <7 years (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.4-7.4), chronic disease (OR, 3.6; 95% CI, 2.6-5.1), recent transplantation (OR, 2.7; 95% CI, 1.3-5.2), and adenovirus type 5 (OR, 2.7; 95% CI, 1.5-4.7) or type 21 infection (OR, 7.6; 95% CI, 2.6-22.3) increased the risk of severe disease.

More than 35 years ago, population-based studies of viral respiratory illnesses among US families were conducted in Ohio [1], Kansas [2], Louisiana [3], New York [4], and Washington [5]. As a result of these investigations, scientists concluded that adenovirus infection was quite common among children. Approximately 50% of infections were asymptomatic, and symptomatic infections were typically mild and resolved without sequelae. In contrast, military populations experienced severe epidemics of acute respiratory disease, including pneumonia and encephalitis, especially involving adenovirus types 4, 7, and 21. For example, in 1958, adenoviral infection was reported to have caused hospitalization of an estimated 10% of military recruits [6] and to be the etiology of most respiratory disease during winter months. Subsequently, vaccines for adenovirus types 4 and 7 were developed and effectively used among US military trainees from the 1970s until the late 1990s [7,8]. Thus, until recently, adenovirus infection was considered to have little consequence, except for causing morbidity among military trainees.

However, much has changed since these early epidemiological studies were conducted. In contrast to the modest number of adenovirus types recognized 35 years ago, 51 unique serotypes are now recognized. Different serotypes have been found to have different tissue tropisms that correlate with different clinical manifestations of infection. Limited epidemiological investigations have revealed that, among some specific serotypes, multiple genetic variants exist that often have quite different geographical distributions and associated virulence [9-11]. In addition, largely because of molecular diagnostics, adenovirus infection has been associated with a number of acute and chronic diseases, including chronic airway obstruction [12] and pulmonary dysplasia [13], myocarditis and dilated cardiomyopathy [14], mononucleosis-like syndromes [15], intussusception [16], sudden infant perinatal death [17], and obesity [18,19]. Among some population groups, adenoviral infection is common and, often, severe. For example, the incidence of adenoviral disease among bone marrow transplant

recipients varies from 3% to 20% [20], and mortality can exceed 50% [21]. Similarly, multiple recent outbreaks of adenoviral infection in the United States have frequently occurred among institutionalized children and in medical settings, resulting in significant morbidity and mortality among patients and medical staff [22]. In vitro studies suggest that specific adenovirus types are more likely to respond to certain antiviral therapies [23]. Finally, since the military lost its manufacturer of adenovirus types 4 and 7 vaccines in the late 1990s, numerous outbreaks of adenovirus infection have occurred among military trainees, resulting in great morbidity [24,25]. Subsequently, the US Department of Defense identified a new vaccine manufacturer, and restoration of adenovirus types 4 and 7 vaccines is projected for 2008 [25]. It seems prudent to investigate whether previously very effective and safe vaccines may also benefit some nonmilitary populations. Therefore, an updated look at the epidemiology of human adenovirus infection is warranted. In this report, we present 25 months of viral and patient epidemiological data on clinical adenovirus infection detected through a nationwide network of 22 US military and civilian medical facilities. We used a recently described molecular adenovirus typing technique to characterize the strains of adenovirus [26].

MATERIALS AND METHODS

Population

From July 2004 through September 2006, specimens that were positive for adenovirus by rapid diagnostic test, PCR, or culture were collected from 22 US medical facilities. Of these facilities, 8 were military sites located in California, Georgia, Illinois, Missouri, New Jersey, South Carolina (2 sites), and Texas, and 14 were civilian laboratories located in Arizona, Colorado, Connecticut, Indiana, Florida, North Carolina, New York (2 sites), Missouri (2 sites), Tennessee, Texas, Washington, and Wisconsin. Samples were collected as part of routine testing, labeled with unique study identifiers, and sent to the University of Iowa Center for Emerging Infectious Diseases (Iowa City) for genetic typing. This study was approved by the multiple institutional review boards representing the participating laboratories.

As part of routine viral respiratory pathogen surveillance [25], the military laboratories first submitted specimens to the Navy Respiratory Disease Laboratory in San Diego, California. Each month, after viral identification work, the Navy laboratory shared a sample set of ~30 specimens with the Center for Emerging Infectious Diseases. This sample set represented specimens that were positive for adenovirus from each of the 8 sites, distributed over time. For adenovirus-positive specimens, the Navy laboratory provided the specimen collection date and the age, sex, and training site of the patient from whom the specimen was obtained.

Civilian laboratories were asked to submit all adenovirus-positive specimens. Limited demographic and clinical data were obtained from each civilian specimen, including the laboratory collection site (city and state), collection date, specimen source (e.g., nasal, pharyngeal or blood), and specimen type (e.g., culture, direct fluorescent antibody, or PCR), as well as patient birth date and sex, whether the patient was hospitalized when the specimen was collected, and whether the patient had undergone transplantation during the 6 months prior to specimen collection. Because of their risk for severe disease, additional information (race and ethnicity, clinical presentation, hospitalization care, disposition, cancer status, and chronic disease status) was obtained from patients with adenovirus infection who were aged <7 years or who had undergone transplantation within 6 months before the positive adenovirus result. The cutoff value of <7 years of age was based on a recent investigation of an outbreak of adenovirus type 7d2 infection (among 93 patients, with a 33% attack rate and 8 deaths), in which children aged <7 years were found to be at increased risk for illness [22].

DNA extraction, PCR, and sequencing

After an initial study, we found that most adenovirus-positive specimens yielded PCR amplification products without requiring additional culture enrichment. Viral DNA was extracted from 200 μL of the original adenovirus-positive specimen in a final elution volume of ~200 μL using the QIAamp DNA Blood Mini Kit (Qiagen). An initial volume of 5 μL of eluted sample was amplified using a PCR procedure that targeted hypervariable regions 1-6 of the hexon gene [26]. M13 universal priming tails (forward, 5′-TGT AAA ACG ACG GCC AGT-3′; and reverse, 5′-CAG GAA ACA GCT ATG ACC-3′) were added to the previously described primers to facilitate sequencing. Expected amplicons from this reaction ranged from 764 to 896 bp in length. These amplicons were then sequenced on a 3730 xl DNA Analyser (Applied BioSystems). The forward and reverse sequences were combined using BioEdit (Ibis Therapeutics) and were compared with the similar sequences of 51 well-characterized prototype viruses and other well-characterized genotypes from our collections and from GenBank. Specimens that yielded identity scores ≥90%, compared with both our internal sequence database and that of GenBank, were considered to be good genotype matches.

Culture

When PCR amplification failed, the original specimen was inoculated into A549 cells (ATCC) and incubated at 37°C for 4-7 days or until a cytopathic effect was observed. If, after 7 days, no cytopathic effect was detected, cells were cultured again. After cytopathic effect was confirmed, the positive cell culture specimen was characterized by PCR and sequencing.

Validation

A systematic sample of 101 adenovirus-positive specimens containing numerous genotypes was shared with the Viral and Rickettsial Disease Laboratory of the California Department of Health Services (Richmond) for blinded validation using classic serotyping techniques. This laboratory shared 3 of these specimens with the Navy Respiratory Disease Laboratory for further study using a PCR adenovirus typing algorithm [27].

Statistical analyses

Questionnaire and laboratory data were linked by the unique specimen number. In instances in which several adenovirus-positive specimens were obtained from the same patient and clinical event, the linkage of these specimens was indicated by the civilian laboratories using study forms. During studies of clinical outcomes, only the first adenovirus-positive specimen was considered in studies of clinical events. The χ^2 test and Fisher's exact test were used to examine potential risk factor associations. The exact Cochran-Armitage test for trend was used to examine adenovirus genotype prevalence across years. Logistic regression modeling was used to examine potential risk factors for outcomes, such as pneumonia. The proportional odds model was used to examine risk factors for severe adenovirus infection, considering the outcomes of hospitalization, intensive care unit stay, and death in a mutually exclusive, ordinal severity scale based on data on the first adenovirus-positive specimen for the clinical event. These 3 final multivariable models were derived using a saturated model and manual backwards elimination. Analyses were performed using SAS, version 9.1 (SAS Institute).

RESULTS

Validation

In the blinded validation study, 98 (97%) of the 101 adenovirus-positive specimens were typeable using type-specific neutralization. Serotyping agreed with genotyping for all 98 specimens. The remaining 3 specimens of unknown types were studied using a novel and quite

different PCR typing algorithm [27], and the blinded results of this algorithm were in agreement with University of Iowa genotyping methods.

Genotyping by PCR and sequencing

During the study period, 2237 adenovirus-positive specimens were received (1653 specimens from civilians and 584 from military trainees). All of the specimens from military trainees resulted from culture. Specimen type information was available for 1170 specimens from civilians; 84.9% of specimens were isolated by culture, 7.9% by direct fluorescent antibody, and 7.2% by PCR assays. Ninety-eight percent of the 2237 adenovirus-positive specimens were successfully typed by PCR and sequencing. Of the 47 initially nontypeable specimens, 27 (57.4%) were eventually typed after statistical analysis had been concluded, 4 (8.5%) were not confirmed to be positive for adenovirus by PCR, and 16 (34.0%) were confirmed to be positive for adenovirus by PCR, but the sequence data were inconclusive. The samples that were not confirmed to be positive for adenovirus by PCR may represent false-positive specimens or specimens with low viral titer that did not yield adenovirus by culture. The samples confirmed to be positive for adenovirus by PCR that had inconclusive sequence data may represent dual adenovirus infections or infection with novel viruses. We are further analyzing these specimens.

The 582 successfully typed specimens from military trainees were comprised primarily of adenovirus hexon sequence genotypes (HSgenotypes) 4 (92.8% of specimens), 3 (2.6%), and 21 (2.4%) (table 1). The age and sex distribution of patients with adenovirus infection were consistent with the demographic characteristics of military training populations. During the study period, there was a statistically significant increasing trend in the prevalence of adenovirus type 21 isolates and a decreasing trend in the prevalence of type 4 isolates. These data represent only a small subset and limited time distribution of adenovirus isolates found in specimens from military trainees. Detailed analyses of a more comprehensive sample set are the subject of a separate report (K.L.R., unpublished data).

Specimens from civilians yielded a more diverse distribution of adenovirus HSgenotypes, with 23 different types detected (table 2). Among the 1608 adenovirus-positive specimens successfully typed, 76.8% were from children aged <7 years, 59% were from male patients, 71.0% were from upper respiratory tract sites, and 49.6% were associated with hospitalization. The most prevalent adenovirus HSgenotypes were types 3 (34.6% of specimens), 2 (24.3%), 1 (17.7%), and 5 (5.3%). The distribution of HSgenotypes differed by age group (with types 1 and 2 being more prevalent among patients aged <7 years) and by specimen source (with types 1, 3, and 2 being most prevalent among blood, upper respiratory tract, and gastrointestinal tract specimens, respectively).

For the 1059 unique clinical events experienced by patients with adenovirus infection who were aged <7 years or who had undergone transplantation within 6 months prior to specimen collection, more clinical information was obtained. Of these patients, 95.3% were aged <7 years, 58.9% were male, 11.0% reported to have recently received a transplant, and 4.2% had received a diagnosis of cancer (table 3). Sixty-seven (57.8%) of the 116 transplant recipients had received a bone marrow transplant (data not shown). Thirty-four (58.8%) of the 45 patients with cancer had cancer of lymphatic and hematopoietic origin (data not shown). Four hundred fifty (42.5%) of the 1059 patients with adenovirus infection presented with upper respiratory tract infection. Two hundred fifty-five patients (24.1%) were hospitalized for ≥4 days (median duration of hospitalization, 3 days). Two hundred eight patients (19.6%) had a chronic disease, and 78 (7.4%) had stayed in an intensive care unit. Because certain populations were thought to be at risk of severe adenovirus infection, the characteristics of patients aged <7 years were stratified by immune status and compared with the characteristics of immunocompromised patients aged ≥7 years (table 4). In general, nonimmunocompromised children aged <7 years

experienced more adenovirus type 3 infections and more upper respiratory tract infections than did immunocompromised children aged <7 years; however, the nonimmunocompromised children had less severe disease and were less likely to have numerous adenovirus isolates per clinical event.

A number of laboratories submitted multiple adenovirus-positive specimens for a single clinical event. Most of these specimens were of the same genotype; however, 20 unique clinical events were found to be associated with laboratory evidence of infection with ≥2 adenovirus HSgenotypes (table 5). Most of these infections involving multiple adenovirus HSgenotypes occurred in immunocompromised patients who were aged <7 years.

The multivariable risk factor modeling (table 6) for adenovirus disease severity (death or intensive care unit stay vs. hospitalization vs. other disease) revealed some interesting findings. As expected, patients aged <7 years (OR, 3.2; 95% CI, 1.4-7.4), patients with chronic disease (OR, 3.6; 95% CI, 2.6-5.1), and patients who had recently undergone transplantation (OR, 2.7; 95% CI, 1.3-5.2) had an increased risk of severe disease. However, unexpectedly, patients infected with adenovirus type 5 (OR, 2.7; 95% CI, 1.5-4.7) or 21 (OR, 7.6; 95% CI, 2.6-22.3) also had a higher risk of developing severe adenovirus disease. Similar multivariable modeling was performed for the outcome of pneumonia, but no specific adenovirus types were associated with this condition (data not shown).

DISCUSSION

Sequencing of hypervariable regions 1-6 of the adenovirus hexon gene [26] appears to correlate well with serological and other molecular methods for typing human adenovirus and, unlike serological methods that can take weeks to perform, can generally be completed within 2 days. It is likely that PCR and sequencing will replace older, classic adenovirus serotyping methods, because PCR and sequencing have the potential to provide rapid results to clinicians and public health officials evaluating and treating specific patients and responding to outbreaks of adenovirus infection. Conversion from classic serotyping to genotyping of adenovirus is not unlike similar recent shifts for the study of group A streptococci [28] and enterovirus [29].

Typing results yielded some interesting observations. The high prevalence of infection with adenovirus type 4 HSgenotypes among patients in the military is consistent with a recent report [25]. However, the increased prevalence of adenovirus type 21 infection among both military and civilian patients was unexpected (tables 1 and 2). Because prevalence figures for adenovirus infection have been known to fluctuate over time, these changes were not significantly alarming. However, adenovirus type 21 infection has caused sporadic outbreaks among military [30-32] and civilian populations [33,34], and changes in prevalence must be evaluated as possible indicators of the emergence of a novel strain. Because of such outbreaks, adenovirus type 21 vaccine development efforts were attempted [30,35,36] but never finalized, because morbidity associated with adenovirus 21 infection has remained low [7]. The high prevalence of hospitalization among the patients with adenovirus infection (table 2) was surprising. This may reflect the desire of clinicians to more frequently determine the etiology of an infection in patients sick enough to merit hospitalization. However, this high prevalence of hospitalization, the significant number of patients with adenovirus infection who require hospitalization in an intensive care unit, and the relatively long duration of hospitalization that is experienced for patients with adenovirus infection reflect the impact on morbidity that adenovirus infection has in US medical care facilities today.

Before this surveillance effort was initiated, adenovirus type 7 infection was predicted to have a strong association with severe morbidity. Worldwide, various adenovirus type 7 genotypes have emerged to cause epidemics and severe disease [9,37-47]. However, thus far in this

surveillance, adenovirus type 7 infection has not been implicated to have a strong association with severe morbidity. This could be because of a stabilization of circulating adenovirus type 7 genotypes in the United States—as was recently apparent in Iowa for the strain adenovirus type 7d2 [10]—with subsequent increases in herd immunity and reductions in adenovirus type 7 infections. Previous reports have noted that outbreaks of adenovirus type 7 infection seem to be sporadic [40,48] and may be the result of the emergence of new type 7 subtypes [9,40, 48].

The association of adenovirus types 5 and 21 with severe disease (table 6) was unexpected. Although adenovirus types 5 and 21 are associated with novel strains [49], epidemics [33,34, 50,51], severe disease [52], and death [53], these observations have been relatively rare. Our data revealed that, of the 13 patients with adenovirus infection who died, 1 had been infected with adenovirus type 5 (1.7% of the patients infected with type 5), and 2 had been infected with type 21 (14.3% of the patients infected with type 21). Although the data supporting these findings are rather sparse, the observations merit continued study.

Additionally interesting was the relatively high number of patients detected as having infections with multiple adenovirus isolates over time, with multiple adenovirus types being identified during a single clinical event (tables 3, 4 and 5). Recent reports regarding repeat adenovirus detections in immunocompromised patients [54] and multiple strains causing concomitant infection in US military trainees [55] seem to reinforce our observation, illustrating the complexities of evaluating adenovirus infection. Molecular typing strategies are thus useful in evaluating adenovirus infection epidemics and individual patients. For instance, a transplant clinician might use molecular typing to discern whether a patient is experiencing a reactivation of a latent adenovirus infection, a nosocomial infection, a community-acquired infection, or a donor-associated adenovirus infection.

This research has a number of limitations. Although a large number of adenovirus-positive specimens were tested in this study, the specimens were collected for diagnostic purposes and, thus, were likely to have been obtained from the most severely affected patients. In addition, although 98% of the specimens were genotyped with good identity score agreements, relying solely on the hypervariable regions of the hexon gene to distinguish strains may cause to be missed other important genetic differences in strains that may correlate better with host immunologic response and strain virulence. For instance, the fiber protein possesses cell receptor binding sites, and alteration of these sites can alter the tissue tropism of an adenovirus [56]. Similarly, genes coding for certain adenovirus early proteins may influence adenovirus cell-to-cell transmission [57]. Thus, the hexon gene sequencing approach will merit further study augmented with other molecular typing methods to reduce the risk of missing important recombinations of adenovirus.

In conclusion, the hexon gene sequence typing strategy used in this study seems to be very useful. Additional studies of such typing in concert with other molecular typing methods are warranted. Molecular methods have the potential to assist clinicians in evaluating and treating specific patients and in aiding public health officials in investigating adenovirus infection epidemics. The suggestion that adenovirus types 3, 5, and 21 may be associated with more frequent or more severe disease, as well as the unexpected lack of such associations with adenovirus type 7, merit further molecular investigation to determine whether there are viral predictors of disease severity. Finally, our findings that clinical adenovirus infection was often associated with hospitalization and that, more often than expected, multiple adenovirus types could be detected add to our new appreciation of the morbidity associated with adenovirus infection.

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Table 1

Distribution of adenovirus hexon sequence genotypes among specimens from patients in military training facilities.

Variable	Total no. of specimens	Adenovirus type, no. (%) of specimens							
		1 (*n* = 1)	2 (*n* = 1)	3 (*n* = 15)	4 (*n* = 540)	5 (*n* = 1)	7 (*n* = 5)	14 (*n* = 5)	21 (*n* = 14)
Collection year									
2004	261	...	1 (0.4)	6 (2.3)	251 (96.2)	...	...	...	3 (1.1)
2005	234	1 (0.4)	...	5 (2.1)	223 (95.3)	...	...	...	5 (2.1)
2006	86	...	...	4 (4.7)	65 (75.6)	1 (1.2)	5 (5.8)	5 (5.8)	6 (7)
Patient age group									
17-19 years	304	...	...	8 (2.6)	287 (94.4)	...	1 (0.3)	2 (0.7)	6 (2)
20-37 years	277	1 (0.4)	1 (0.4)	7 (2.5)	252 (91)	1 (0.4)	4 (1.4)	3 (1.1)	8 (2.9)
Patient sex									
Male	510	1 (0.2)	...	12 (2.4)	474 (92.9)	...	4 (0.8)	5 (1)	14 (2.7)
Female	61	...	1 (1.6)	3 (4.9)	55 (90.2)	1 (1.6)	1 (1.6)	...	...
Collection site									
Great Lakes, IL	141	...	...	...	137 (97.2)	1 (0.7)	...	2 (1.4)	1 (0.7)
San Diego, CA	91	...	...	...	90 (98.9)	...	...	1 (1.1)	...
Ft. Jackson, SC	86	...	1 (1.2)	6 (7)	78 (90.7)	...	1 (1.2)	...	...
Ft. Leonard Wood, MO	81	...	...	3 (3.7)	72 (88.9)	...	4 (4.9)	...	2 (2.5)
Ft. Benning, GA	65	...	...	6 (9.2)	55 (84.6)	...	...	2 (3.1)	2 (3.1)
Parris Island, SC	64	...	...	...	57 (89.1)	...	...	...	7 (10.9)
Cape May, NJ	33	...	...	...	33 (100)	...	...	...	...
San Antonio, TX	21	1 (4.8)	...	...	18 (85.7)	...	...	...	2 (9.5)

NOTE. Because of missing data, total counts are not always identical.

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Table 2

Distribution of the most prevalent adenovirus hexon sequence genotypes among specimens from the studied civilians.

Variable	Total no. of specimens	Adenovirus type, no. (%) of specimens								
		1 (*n* = 284)	2 (*n* = 390)	3 (*n* = 556)	4 (*n* = 78)	5 (*n* = 86)	7 (*n* = 48)	21 (*n* = 32)	41 (*n* = 29)	Other (*n* = 105)
Collection year										
2004	307	40 (13)	69 (22.5)	132 (43)	20 (6.5)	20 (6.5)	0 (0)	3 (1)	3 (1)	20 (6.5)
2005	846	153 (18.1)	212 (25.1)	293 (34.6)	34 (4)	45 (5.3)	23 (2.7)	18 (2.1)	18 (2.1)	50 (5.9)
2006	455	91 (20)	109 (24)	131 (28.8)	24 (5.3)	21 (4.6)	25 (5.5)	11 (2.4)	8 (1.8)	35 (7.7)
Collection month										
January	197	32 (16.2)	48 (24.4)	71 (36)	6 (3)	8 (4.1)	8 (4.1)	2 (1)	6 (3)	16 (8.1)
February	163	39 (23.9)	34 (20.9)	56 (34.4)	5 (3.1)	11 (6.7)	4 (2.5)	3 (1.8)	4 (2.5)	7 (4.3)
March	168	33 (19.6)	44 (26.2)	50 (29.8)	7 (4.2)	7 (4.2)	6 (3.6)	3 (1.8)	3 (1.8)	15 (8.9)
April	141	31 (22)	38 (27)	39 (27.7)	6 (4.3)	10 (7.1)	6 (4.3)	3 (2.1)	0 (0)	8 (5.7)
May	95	14 (14.7)	24 (25.3)	28 (29.5)	7 (7.4)	3 (3.2)	6 (6.3)	11 (11.6)	2 (2.1)	0 (0)
June	105	18 (17.1)	24 (22.9)	37 (35.2)	6 (5.7)	8 (7.6)	1 (1)	3 (2.9)	1 (1)	7 (6.7)
July	102	11 (10.8)	28 (27.5)	40 (39.2)	5 (4.9)	3 (2.9)	2 (2)	2 (2)	4 (3.9)	7 (6.9)
August	106	8 (7.5)	18 (17)	42 (39.6)	15 (14.2)	7 (6.6)	4 (3.8)	1 (0.9)	1 (0.9)	10 (9.4)
September	77	17 (22.1)	10 (13)	32 (41.6)	7 (9.1)	3 (3.9)	2 (2.6)	0 (0)	0 (0)	6 (7.8)
October	84	17 (20.2)	14 (16.7)	30 (35.7)	5 (6)	6 (7.1)	2 (2.4)	0 (0)	3 (3.6)	7 (8.3)
November	189	35 (18.5)	48 (25.4)	68 (36)	4 (2.1)	13 (6.9)	3 (1.6)	3 (1.6)	1 (0.5)	14 (7.4)
December	181	29 (16)	60 (33.1)	63 (34.8)	5 (2.8)	7 (3.9)	4 (2.2)	1 (0.6)	4 (2.2)	8 (4.4)
Patient age group										
<7 years	1235	253 (20.5)	334 (27)	419 (33.9)	38 (3.1)	64 (5.2)	34 (2.8)	13 (1.1)	25 (2)	55 (4.5)
≥7 years	373	31 (8.3)	56 (15)	137 (36.7)	40 (10.7)	22 (5.9)	14 (3.8)	19 (5.1)	4 (1.1)	50 (13.4)
Patient sex										
Male	948	182 (19.2)	228 (24.1)	305 (32.2)	53 (5.6)	49 (5.2)	27 (2.8)	21 (2.2)	12 (1.3)	71 (7.5)
Female	653	102 (15.6)	156 (23.9)	251 (38.4)	25 (3.8)	37 (5.7)	21 (3.2)	11 (1.7)	16 (2.5)	34 (5.2)
Collection site										
New Haven, CT	201	44 (21.9)	33 (16.4)	70 (34.8)	19 (9.5)	15 (7.5)	4 (2)	9 (4.5)	0 (0)	7 (3.5)
Indianapolis, IN	178	27 (15.2)	30 (16.9)	57 (32)	3 (1.7)	18 (10.1)	9 (5.1)	0 (0)	9 (5.1)	25 (14)
St. Louis, MO	178	42 (23.6)	47 (26.4)	60 (33.7)	7 (3.9)	12 (6.7)	1 (0.6)	6 (3.4)	0 (0)	3 (1.7)
Denver, CO	162	40 (24.7)	44 (27.2)	36 (22.2)	6 (3.7)	4 (2.5)	6 (3.7)	2 (1.2)	5 (3.1)	19 (11.7)
Houston, TX	138	16 (11.6)	50 (36.2)	44 (31.9)	9 (6.5)	6 (4.3)	3 (2.2)	0 (0)	3 (2.2)	7 (5.1)
Manhasset, NY	120	16 (13.3)	33 (27.5)	50 (41.7)	14 (11.7)	3 (2.5)	1 (0.8)	1 (0.8)	0 (0)	2 (1.7)
Tempe, AZ	119	19 (16)	24 (20.2)	60 (50.4)	2 (1.7)	3 (2.5)	6 (5)	1 (0.8)	1 (0.8)	3 (2.5)
Kansas City, MO	107	8 (7.5)	12 (11.2)	68 (63.6)	3 (2.8)	2 (1.9)	6 (5.6)	0 (0)	3 (2.8)	5 (4.7)
Milwaukee, WI	103	11 (10.7)	43 (41.7)	19 (18.4)	0 (0)	6 (5.8)	1 (1)	0 (0)	5 (4.9)	18 (17.5)
Nashville, TN	78	7 (9)	16 (20.5)	27 (34.6)	3 (3.8)	3 (3.8)	1 (1.3)	11 (14.1)	1 (1.3)	9 (11.5)
Seattle, WA	73	10 (13.7)	18 (24.7)	30 (41.1)	3 (4.1)	6 (8.2)	0 (0)	0 (0)	1 (1.4)	5 (6.8)
Chapel Hill, NC	69	24 (34.8)	17 (24.6)	10 (14.5)	5 (7.2)	4 (5.8)	7 (10.1)	0 (0)	0 (0)	2 (2.9)
Syracuse, NY	54	18 (33.3)	16 (29.6)	10 (18.5)	4 (7.4)	3 (5.6)	1 (1.9)	1 (1.9)	1 (1.9)	0 (0)
Jacksonville, FL	28	2 (7.1)	7 (25)	15 (53.6)	0 (0)	1 (3.6)	2 (7.1)	1 (3.6)	0 (0)	0 (0)
Specimen source										
Upper respiratory tract	1142	215 (18.8)	282 (24.7)	461 (40.4)	57 (5)	55 (4.8)	26 (2.3)	21 (1.8)	2 (0.2)	23 (2)
Lower respiratory tract	58	6 (10.3)	12 (20.7)	16 (27.6)	5 (8.6)	5 (8.6)	1 (1.7)	6 (10.3)	1 (1.7)	6 (0.1)
Gastrointestinal tract	234	34 (14.5)	65 (27.8)	36 (15.4)	10 (4.3)	20 (8.6)	6 (2.6)	3 (1.3)	26 (11.1)	34 (0.1)
Urine	44	2 (4.6)	6 (13.6)	3 (6.8)	1 (2.3)	2 (4.6)	4 (9.1)	0 (0)	0 (0)	26 (0.6)
Blood	37	18 (48.7)	7 (18.9)	2 (5.4)	0 (0)	2 (5.4)	6 (16.2)	0 (0)	0 (0)	2 (0.1)
Ocular	36	0 (0)	1 (2.8)	22 (61.1)	3 (8.3)	0 (0)	1 (2.8)	1 (2.8)	0 (0)	8 (0.2)
Other[a]	57	9 (15.8)	17 (29.8)	16 (28.1)	2 (3.5)	2 (3.5)	4 (7)	1 (1.8)	0 (0)	6 (0.1)
Patient hospitalized when culture obtained										
Yes	798	115 (14.4)	198 (24.8)	247 (31)	40 (5)	49 (6.1)	28 (3.5)	26 (3.3)	20 (2.5)	75 (9.4)
No	718	155 (21.6)	171 (23.8)	269 (37.5)	35 (4.9)	32 (4.5)	15 (2.1)	6 (0.8)	9 (1.3)	26 (3.6)

Variable	Total no. of specimens	Adenovirus type, no. (%) of specimens								
		1 (*n* = 284)	2 (*n* = 390)	3 (*n* = 556)	4 (*n* = 78)	5 (*n* = 86)	7 (*n* = 48)	21 (*n* = 32)	41 (*n* = 29)	Other (*n* = 105)
Uncertain	92	14 (15.2)	21 (22.8)	40 (43.5)	3 (3.3)	5 (5.4)	5 (5.4)	0 (0)	0 (0)	4 (4.3)

NOTE. Counts occasionally include multiple isolates from a single clinical event. Because of missing data, total counts are not always identical.

[a] Includes CSF, lymph nodes, combined sources, and no source indicated.

Table 3

Medical record information based on a unique clinical event associated with a adenovirus-positive specimen for patients aged <7 years or patients who had received a transplant within 6 months prior to specimen collection (no duplicate isolates).

Variable	Total no. of unique clinical events	Adenovirus hexon sequence genotype, no. (%) of unique clinical events								
		1 (*n* = 226)	2 (*n* = 282)	3 (*n* = 351)	4 (*n* = 31)	5 (*n* = 59)	7 (*n* = 30)	21 (*n* = 14)	41 (*n* = 16)	Other (*n* = 50)
Patient age group										
<7 years	1009	215 (21.3)	275 (27.3)	346 (34.3)	29 (2.9)	53 (5.3)	29 (2.9)	12 (1.2)	15 (1.5)	35 (3.5)
≥7 years	50	11 (22)	7 (14)	5 (10)	2 (4)	6 (12)	1 (2)	2 (4)	1 (2)	15 (30)
Patient sex										
Male	624	138 (22.1)	170 (27.2)	195 (31.3)	21 (3.4)	34 (5.4)	16 (2.6)	8 (1.3)	7 (1.1)	35 (5.6)
Female	435	88 (20.2)	112 (25.7)	156 (35.9)	10 (2.3)	25 (5.7)	14 (3.2)	6 (1.4)	9 (2.1)	15 (3.4)
Immunocompromization										
Cancer	7	0 (0)	4 (57.1)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (14.3)
Cancer and transplantation	38	5 (13.2)	10 (26.3)	5 (13.2)	1 (2.6)	1 (2.6)	3 (7.9)	1 (2.6)	1 (2.6)	11 (28.9)
Nothing reported	936	203 (21.7)	252 (26.9)	332 (35.5)	28 (3)	48 (5.1)	25 (2.7)	12 (1.3)	11 (1.2)	25 (2.7)
Transplantation	78	18 (23.1)	16 (20.5)	13 (16.7)	2 (2.6)	10 (12.8)	2 (2.6)	1 (1.3)	3 (3.8)	13 (16.7)
Upper respiratory tract infection										
Yes	450	109 (24.2)	128 (28.4)	154 (34.2)	11 (2.4)	27 (6)	8 (1.8)	4 (0.9)	1 (0.2)	8 (1.8)
Not reported	609	117 (19.2)	154 (25.3)	197 (32.3)	20 (3.3)	32 (5.3)	22 (3.6)	10 (1.6)	15 (2.5)	42 (6.9)
Pneumonia										
Yes	98	16 (16.3)	27 (27.6)	35 (35.7)	4 (4.1)	5 (5.1)	3 (3.1)	2 (2)	1 (1)	5 (5.1)
Not reported	961	210 (21.9)	255 (26.5)	316 (32.9)	27 (2.8)	54 (5.6)	27 (2.8)	12 (1.2)	15 (1.6)	45 (4.7)
Conjunctivitis										
Yes	70	7 (10)	9 (12.9)	41 (58.6)	7 (10)	3 (4.3)	1 (1.4)	0 (0)	0 (0)	2 (2.9)
Not reported	989	219 (22.1)	273 (27.6)	310 (31.3)	24 (2.4)	56 (5.7)	29 (2.9)	14 (1.4)	16 (1.6)	48 (4.9)
Encephalitis										
Yes	4	1 (25)	0 (0)	2 (50)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
Not reported	1055	225 (21.3)	282 (26.7)	349 (33.1)	31 (2.9)	59 (5.6)	29 (2.7)	14 (1.3)	16 (1.5)	50 (4.7)
Duration of hospital stay										
Not recorded	32	4 (12.5)	6 (18.8)	18 (56.3)	0 (0)	3 (9.4)	1 (3.1)	0 (0)	0 (0)	0 (0)
No stay or unknown[a]	460	111 (24.1)	123 (26.7)	164 (35.7)	13 (2.8)	17 (3.7)	12 (2.6)	2 (0.4)	6 (1.3)	12 (2.6)
up to 3 days	300	74 (24.7)	82 (27.3)	103 (34.3)	9 (3)	13 (4.3)	7 (2.3)	3 (1)	1 (0.3)	8 (2.7)
4-407 days	255	35 (13.7)	68 (26.7)	63 (24.7)	8 (3.1)	26 (10.2)	9 (3.5)	9 (3.5)	9 (3.5)	28 (11)
Unknown no. of days	12	2 (16.7)	3 (25)	3 (25)	1 (8.3)	0 (0)	1 (8.3)	0 (0)	0 (0)	2 (16.7)
Duration of intensive care unit stay										
Not recorded	3	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No stay or unknown[a]	973	209 (21.5)	261 (26.8)	331 (34)	29 (3)	48 (4.9)	26 (2.7)	8 (0.8)	15 (1.5)	46 (4.7)
1-8 days	39	9 (23.1)	9 (23.1)	9 (23.1)	1 (2.6)	6 (15.4)	1 (2.6)	2 (5.1)	1 (2.6)	1 (2.6)
9-326 days	39	7 (17.9)	9 (23.1)	7 (17.9)	1 (2.6)	5 (12.8)	3 (7.7)	4 (10.3)	0 (0)	3 (7.7)
Unknown no. of days	5	0 (0)	2 (40)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cause of death										
Not recorded	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
None or unknown[a]	1046	225 (21.5)	276 (26.4)	350 (33.5)	31 (3)	58 (5.5)	29 (2.8)	12 (1.1)	16 (1.5)	49 (4.7)
Other unknown cause	6	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)
Primarily adenovirus infection	6	1 (16.7)	3 (50)	0 (0)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	0 (0)	0 (0)
Chronic disease										
Not recorded	31	6 (19.4)	7 (22.6)	14 (45.2)	1 (3.2)	1 (3.2)	1 (3.2)	0 (0)	0 (0)	1 (3.2)
No	732	152 (20.8)	201 (27.5)	249 (34)	22 (3)	41 (5.6)	21 (2.9)	8 (1.1)	8 (1.1)	30 (4.1)
Yes	208	49 (23.6)	56 (26.9)	49 (23.6)	7 (3.4)	11 (5.3)	5 (2.4)	6 (2.9)	6 (2.9)	19 (9.1)
Unknown	88	19 (21.6)	18 (20.5)	39 (44.3)	1 (1.1)	6 (6.8)	3 (3.4)	0 (0)	2 (2.3)	0 (0)
No. of adenovirus-positive specimens per clinical event[b]										

Variable	Total no. of unique clinical events	Adenovirus hexon sequence genotype, no. (%) of unique clinical events								
		1 (*n* = 226)	2 (*n* = 282)	3 (*n* = 351)	4 (*n* = 31)	5 (*n* = 59)	7 (*n* = 30)	21 (*n* = 14)	41 (*n* = 16)	Other (*n* = 50)
1	980	219 (22.3)	263 (26.8)	328 (33.5)	26 (2.7)	55 (5.6)	23 (2.3)	12 (1.2)	13 (1.3)	41 (4.2)
2	44	4 (9.1)	10 (22.7)	16 (36.4)	2 (4.5)	3 (6.8)	2 (4.5)	2 (4.5)	2 (4.5)	3 (6.8)
3	22	1 (4.5)	5 (22.7)	6 (27.3)	3 (13.6)	0 (0)	2 (9.1)	0 (0)	0 (0)	5 (22.7)
4	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	4	0 (0)	0 (0)	1 (25)	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	1 (25)
6	3	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (33.3)	0 (0)
7	2	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
9	2	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)

[a] "Unknown" was a given response on the data forms.

[b] No. of adenovirus-positive specimens per clinical event refers to the number of specimens submitted that were associated with a single clinical event for a unique patient on the basis of medical record review at the submitting laboratory.

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Table 4

Medical and genotyping information for adenovirus-infected patients per unique clinical event for patients aged <7 years or patients who had received a transplant within 6 months before specimen collection (no duplicate isolates), by age group and immunocompromization status.

Variable	No. (%) of unique clinical events		
	Patients aged <7 years		Immunocompromised patients aged ≥7 years (*n* = 50)
	Immunocompromised (*n* = 73)	Nonimmunocompromised (*n* = 936)	
Serotype			
1	12 (16.4)	203 (21.7)	11 (22)
2	23 (31.5)	252 (26.9)	7 (14)
3	14 (19.2)	332 (35.5)	5 (10)
4	1 (1.4)	28 (3)	2 (4)
5	5 (6.9)	48 (5.1)	6 (12)
6	2 (2.7)	7 (0.8)	0 (0)
7	4 (5.5)	25 (2.7)	1 (2)
11	1 (1.4)	0 (0)	6 (12)
12	3 (4.1)	1 (0.1)	0 (0)
14	0 (0)	3 (0.3)	0 (0)
15	1 (1.4)	0 (0)	0 (0)
19	0 (0)	7 (0.8)	1 (2)
21	0 (0)	12 (1.3)	2 (4)
22	0 (0)	1 (0.1)	0 (0)
25	0 (0)	1 (0.1)	0 (0)
31	3 (4.1)	4 (0.4)	2 (4)
34	0 (0)	0 (0)	4 (8)
35	0 (0)	1 (0.1)	2 (4)
41	4 (5.5)	11 (1.2)	1 (2)
Sex			
Male	42 (57.5)	550 (58.8)	32 (64)
Female	31 (42.5)	386 (41.2)	18 (36)
Upper respiratory tract infection			
Not reported	60 (82.2)	503 (53.7)	46 (92)
Yes	13 (17.8)	433 (46.3)	4 (8)
Pneumonia			
Not reported	71 (97.3)	845 (90.3)	45 (90)
Yes	2 (2.7)	91 (9.7)	5 (10)
Conjunctivitis			
Not reported	73 (100)	866 (92.5)	50 (100)
Yes	0 (0)	70 (7.5)	0 (0)
Encephalitis			
Not reported	72 (98.6)	933 (99.7)	50 (100)
Yes	1 (1.4)	3 (0.3)	0 (0)
Duration of hospital stay			
Not recorded	26 (35.6)	6 (0.6)	0 (0)
No stay or unknown[a]	11 (15.1)	432 (46.2)	17 (34)
Up to 3 days	5 (6.9)	293 (31.3)	2 (4)
4-407 days	30 (41.1)	194 (20.7)	31 (62)
Unknown no. of days	1 (1.4)	11 (1.2)	0 (0)
Duration of intensive care unit stay			
Not recorded	0 (0)	3 (0.3)	0 (0)
No stay or unknown[a]	64 (87.7)	867 (92.6)	42 (84)
1-8 days	1 (1.4)	34 (3.6)	4 (8)
9-326 days	8 (11)	28 (3)	3 (6)
Unknown no. of days	0 (0)	4 (0.4)	1 (2)
Cause of death			

Variable	No. (%) of unique clinical events		
	Patients aged <7 years		Immunocompromised patients aged ≥7 years (*n* = 50)
	Immunocompromised (*n* = 73)	Nonimmunocompromised (*n* = 936)	
Not recorded	0 (0)	1 (0.1)	0 (0)
None or unknown[a]	69 (94.5)	931 (99.5)	46 (92)
Other or unknown cause	1 (1.4)	3 (0.3)	2 (4)
Primarily adenovirus infection	3 (4.1)	1 (0.1)	2 (4)
Chronic disease			
Not recorded	2 (2.7)	29 (3.1)	0 (0)
No	14 (19.2)	706 (75.4)	12 (24)
Yes	24 (32.9)	149 (15.9)	35 (70)
Unknown	33 (45.2)	52 (5.6)	3 (6)
Number of adenovirus-positive specimens per clinical event			
1	51 (69.9)	893 (95.4)	36 (72)
2	5 (6.9)	34 (3.6)	5 (10)
3	10 (13.7)	9 (1)	3 (6)
≥4[b]	7 (9.6)	0 (0)	6 (12)

[a] "Unknown" was a given response on the data forms.

[b] Participants had up to 20 unique adenovirus types detected.

Table 5

Data on patients whose collected specimen yielded ≥2 adenovirus hexon sequence genotypes for a single clinical event.

	Patient information			Isolate information		
Clinical event	Age	Transplant	Cancer	Collection month/year	Adenovirus type	No. of isolates
1	2	Pancreas and small bowel	None	1/2005 1/2005	2 5	2 1
2	4	Bone marrow	None	1/2005 2/2005 3/2005	41 41 2	1 4 1
3	9	Bone marrow	Lymphatic and hematopoietic tissue	11/2004 10/2004 12/2004	2 3 2	3 1 1
4	4	Bone marrow	Lymphatic and hematopoietic tissue	11/2005 11/2005 11/2005 11/2005	18 7 6 15	1 1 2 1
5	5	Bone marrow	None	1/2006 1/2006	2 3	1 1
6	43	None	None	6/2005 6/2005	1 2	2 1
7	27	Bone marrow	None	1/2006 1/2006 2/2006 2/2006	2 7 1 2	3 1 1 1
8	52	Kidney	None	10/2005 10/2005 11/2005	2 6 NT	1 1 1
9	3	Bone marrow	Lymphatic and hematopoietic tissue	11/2005 10/2005 10/2005 9/2005 9/2005 9/2005	1 1 NT 1 NT 7	4 8 1 5 1 1
10	3	Bone marrow	Lymphatic and hematopoietic tissue	12/2005 1/2006	1 3	1 1
11	3	Bone marrow	Lymphatic and hematopoietic tissue	7/2005 8/2005 8/2005 8/2005 8/2005 8/2005 8/2005	2 NT 2 NT 1 NT NT	2 1 2 1 1 1 1
12	0	None	None	4/2006 3/2006 3/2006	19 19 7	1 1 1
13	4	Bone marrow	None	5/2006 5/2006	3 1	1 2
14	2	Bone marrow	Medulloblastoma	3/2006 2/2006	3 4	1 2

Clinical event	Patient information			Isolate information		
	Age	Transplant	Cancer	Collection month/year	Adenovirus type	No. of isolates
15	2	Bone marrow	Lymphatic and hematopoietic tissue	12/2005 12/2005 3/2006 1/2006 3/2006 4/2006	3 2 1 2 41 2	1 1 1 1 1 1
16	5	Bone marrow	Lymphatic and hematopoietic tissue	12/2005 12/2005 12/2005 12/2005	6 3 6 7	2 1 1 1
17	4	None	Lymphatic and hematopoietic tissue	9/2005 9/2005 10/2005	2 6 6	1 1 1
18	17	None	Bone, connective tissue, skin, or breast	5/2006 6/2006	7 35	2 1
19	9	None	Lymphatic and hematopoietic tissue	8/2004 8/2004	3 4	1 1
20	6	Bone marrow	None	1/2005 7/2005 8/2005	7 15 7	1 1 1

NOTE. NT, nontyped adenovirus.

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Table 6

Risk factors for adenovirus clinical severity on the basis of the proportional odds model.

	Severity level				
	Sample distribution			OR (95% CI)	
Variables	Death or ICU stay	Hospitalization	Other	Unadjusted	Adjusted[a]
Age group					
<7 years	76	456	449	0.5 (0.3-0.8)	3.2 (1.4-7.4)
≥7 years	9	24	17	Reference	Reference
Adenovirus hexon sequence genotype					
1	16	94	111	1.1 (0.8-1.5)	0.9 (0.7-1.3)
2	22	130	123	1.3 (1-1.8)	1.1 (0.8-1.6)
3	19	150	170	Reference	Reference
4	2	16	13	1.4 (0.7-2.9)	1.1 (0.6-2.3)
5	11	28	17	2.5 (1.5-4.3)	2.7 (1.5-4.7)
7	4	13	12	1.6 (0.8-3.3)	1.4 (0.7-3)
21	6	6	2	10.3 (3.6-29.2)	7.6 (2.6-22.3)
41	1	9	6	1.7 (0.6-4.4)	1 (0.4-2.7)
Other	4	34	12	2.6 (1.5-4.7)	1.8 (0.9-3.3)
Chronic disease					
Yes	40	123	45	4.1 (3-5.5)	3.6 (2.6-5.1)
No or unknown	45	357	421	Reference	Reference
Transplantation during the 6 months previous to specimen collection					
Yes	19	44	24	2.8 (1.8-4.2)	2.7 (1.3-5.2)
No or unknown	66	436	442	Reference	Reference

NOTE. The model included only the first adenovirus isolate per unique medial event. Only isolates that were genotyped were considered. Adenovirus severity was classified as an ordinal outcome (death or ICU stay or hopitalization vs. other illness). ICU, intensive care unit.

[a] Statistically significant covariates, after manual backward elimination from a saturated model. The adjusted model included only the variables shown.