Health Care Transmission of a Newly Emergent Adenovirus Serotype in Health Care Personnel at a Military Hospital in Texas, 2007

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Background. Adenoviruses can cause outbreaks of febrile respiratory illness in military trainees, but until 2007, adenovirus serotype 14 (Ad14) was never associated with such outbreaks. From April through June 2007, 15 trainees at one base were hospitalized for pneumonia due to Ad14. Subsequent reports of febrile respiratory illness among health care personnel suggested nosocomial transmission.

Methods. Health care personnel participants completed a questionnaire and provided blood and nasal wash specimens for Ad14 diagnostic testing. We defined a confirmed case of Ad14 infection as one with titers ≥1:80 or nasal wash specimens positive for Ad14 by polymerase chain reaction, whereas a possible case was defined by titers of 1:20 or 1:40. We also collected environmental samples.

Results. Among 218 tested health care personnel, 35 (16%) had titers ≥1:20; of these, 7 had possible cases and 28 had confirmed cases of infection. Confirmed case patients were more likely to report febrile respiratory illness (57% vs 11%; P < .001) and to have had direct contact with patients with Ad14 infection (82% vs 62%; P = .04). Of the 23 confirmed case patients with direct contact with Ad14-infected patients, 52% reported that patients were not in contact and droplet precautions at the time of exposure. Ad14 was recovered from several hospital surfaces.

Conclusion. Our findings of possible nosocomial transmission of Ad14 highlight the need to reinforce infection control guidelines.

Human adenoviruses (Ads) cause a broad spectrum of clinical diseases that can range from asymptomatic or mild to severe and life-threatening infections. There are 51 Ad serotypes currently recognized that are classified into 6 species, A–F. The pattern of illness associated with Ad infections tends to be species and/or serotype specific [1–3]. For example, Ad3, Ad4, and Ad7 are the most common serotypes associated with outbreaks of febrile respiratory illness in military trainees; Ad8, Ad19, and Ad37 are associated with outbreaks of keratoconjunctivitis; Ad11 is associated with hemorrhagic cystitis; and Ad40 and Ad41 are associated with acute gastroenteritis.

Ad-associated febrile respiratory illness was a sufficiently important problem for the military that vaccines for the 2 most common serotypes, Ad4 and Ad7, were developed and used from 1971 through 1996, when production of these vaccines was discontinued [4–6]. Ongoing surveillance conducted in 8 United States (US) military training facilities showed that from 1999, when vaccines supply was completely depleted, through 2004, ∼67% of the 22,000 cases of febrile respiratory illness...
per year among military trainees have been caused by Ads [7]. This rate is very similar to the prevaccination era, when Ad was consistently isolated from 30%–70% of military trainees with febrile respiratory illness [8, 9], but very different from when vaccine was in use and Ad-specific disease rates decreased by 95%–99%, reducing febrile respiratory illness rates by 50%–60% [6, 7, 10, 11]. Although numerous Ad serotypes can cause febrile respiratory illness, data from this same surveillance showed that Ad4 was responsible for the vast majority of cases from 2002 through 2005 (95%), although Ad3, Ad7, and Ad21 were occasionally detected in patients with febrile respiratory illness [12].

Although Ads are a major cause of infectious disease hospitalization in US military trainees [13] and can be rapidly spread in closed environments through respiratory secretions and potentially through contaminated surfaces [14–18], Ad transmission in military health care settings has not been commonly reported in the literature. In March 2007, military officials noted a 3-fold increase in weekly febrile respiratory illness rates among military trainees at a Texas Air Force base. Febrile respiratory illness rates remained elevated into July. Ad14, a serotype rarely reported worldwide and not previously reported to be associated with respiratory disease outbreaks in US military trainees, was identified as the predominant etiology of these infections. As a result of this outbreak, 15 trainees were hospitalized for Ad14 pneumonia in the acute care facility on the military base from April though June 2007. Three of these trainees were admitted to intensive care units, and 1 died. Subsequent reports of febrile respiratory illness among health care personnel (HCP) at this facility suggested possible nosocomial spread of Ad14, and an investigation was initiated to assess rates of Ad14 infection among HCP, identify risk factors associated with Ad14 acquisition, and recommend control measures.

**METHODS**

**Study population.** We defined HCP as employees or contractors at the military hospital, including physicians, students, nurses, respiratory therapists, and clerical and housekeeping staff. HCP who worked in the hospital units where trainees with Ad14 pneumonia were admitted from 1 April through 14 June 2007 were identified through a survey of unit chiefs. Because respiratory therapists, attending physicians, medical residents, and housekeepers rotate among different units in the hospital, we obtained a complete list of these employees from supervisors. Identified HCP were informed about the investigation by their supervisors or by the investigation team through face-to-face communication, e-mail messages, flyers, or phone calls, or during employees’ routine team meetings and were asked to participate in the study by completing an anonymous questionnaire and providing blood and nasal wash specimens for Ad14 diagnostic testing. To facilitate HCP participation, a laboratory collection station was set up in each of the hospital units of interest. Personnel were available for collection of clinical specimens at the beginning and end of every shift and during lunch time for 10 consecutive days. HCP who were tested completed a questionnaire that was linked to clinical specimens through the use of a unique identifier.

To assess the prevalence of Ad14 infection among people who worked at the base but were neither HCP nor military trainees, we offered testing for Ad14 infection to a group of environmental engineers at 1 building at the base (control group). Workers who agreed to be tested had blood and nasal wash specimens collected.

**HCP questionnaire.** We used a standardized questionnaire to collect data on demographic characteristics, occupation, comorbidities, history of fever, and respiratory symptoms (eg, cough and sore throat) in the previous 4 months (from March through June 2007) before the study began (9 June 2007); the questionnaire also collected information regarding isolation precautions for patients with Ad14 infection at the time of exposure, exposure characteristics, use of personal protective equipment, hand-washing practices, and exposures to respiratory illness outside of the hospital (eg, at home).

**Environmental sampling.** We sampled frequently touched surfaces in rooms of patients with Ad14 infection (eg, bedrails, patient cabinets, roll-over tables, and infusion pumps) while patients were still in the room and after their discharge from the hospital (ie, after terminal cleaning was complete), as well as surfaces in the emergency department where Ad14 patients were admitted. We also sampled surfaces such as monitors, keyboards, faucet handles, and binders at nursing stations of units where patients with Ad14 infection were admitted. We used swabs moistened with sterile saline solution to wipe surfaces in a 2 × 2 square fashion. For better coverage of sampling area, surfaces were swabbed horizontally, vertically, and diagonally. After collection, swabs were immersed in viral transport medium and frozen at −70°C until shipment on dry ice to the Centers for Disease Control and Prevention (CDC) for processing.

**Laboratory testing.** Specimens were collected from 14 June through 21 June 2007. Nasal wash samples were tested at the Advanced Diagnostics Laboratory at the military base in Texas with use of 2 TaqMan real-time polymerase chain reaction (PCR) assays (Applied Biosystems), 1 of which detects all human adenovirus serotypes [19] and 1 that was designed by CDC to detect only Ad14 [20]. We tested serum specimens at the CDC for the presence of Ad14-neutralizing antibodies by a modified microneutralization assay using an Ad14 outbreak isolate, as described elsewhere [21, 22].
We tested environmental samples at the CDC by real-time PCR assay, as noted above. PCR was performed on total nucleic acids extracted from 300 μL of swab sample with use of the NucliSENS easyMAG (bioMérieux). Samples were spiked with a low copy number DNA plasmid and a parallel PCR was performed to monitor for extraction efficiency and presence of PCR inhibitors. Samples that were positive for Ad DNA were inoculated into A549 cells and monitored for 10 days for cytopathic effect; all cultures were blind-passaged once and held for an additional 10 days before final results were reported.

**Definitions.** We defined positivity for Ad14 as the presence of any Ad14-neutralizing antibody or detection of Ad14 through PCR. Confirmed cases of Ad14 infection were defined as those with Ad14-neutralizing antibody titers ≥1:80 or those that were positive for Ad14 by PCR. Possible cases of Ad14 infection were defined as those that were negative by PCR but had a neutralizing antibody titer of 1:20 or 1:40. Finally, we defined non-cases of Ad14 infection as those that were negative by PCR and had neutralizing antibody titers of <1:20. Febrile respiratory illness was defined as fever (temperature, ≥38.3°C) with respiratory symptoms of cough or sore throat.

**Statistical analysis.** We performed statistical analyses using SAS, version 9.1.3 (SAS Institute). Categorical variables were compared using χ² or Fisher exact test when cells included <10 cases. We defined statistical significance as *P* < .05.

**Ethics.** This investigation was reviewed by human subject personnel at the CDC and was determined to be an urgent public health response. Participation was voluntary and participants gave verbal consent before answering the questionnaire or undergoing specimen collection for Ad14 testing. None of the specimens collected or questionnaires completed had personal identifiers. Specimens were discarded after Ad14 testing was completed.

**RESULTS**

**Cohort of HCP.** Among the 483 HCP identified, 218 (45%) agreed to be tested. Forty-two had positive results for Ad14: 36 (85%) by serology, 2 (5%) by PCR, and 4 (10%) by both. On the basis of serologic titers and PCR results, 7 (3%) of the 42 had antibody titers of 1:10 and were classified as non-cases, 7 (3%) as possible cases, and 28 (13%) as confirmed cases. Patients with possible and confirmed cases combined had a median age of 29 years (range, 19–74 years), and 54% were women.

From March through June 2007, 25 (89%) of the 28 confirmed case patients reported respiratory symptoms (eg, cough or sore throat), and of those, 16 (64%) additionally reported fever. Of the 7 possible case patients, 4 (57%) had respiratory symptoms, and of those, none had fever. Fourteen (88%) of the 16 confirmed case patients with febrile respiratory illness continued working during the course of their illness. Of the 14 symptomatic, confirmed case patients who were not excluded from duty, 9 (64%) were nurses, 3 (22%) were medical technicians, 1 (7%) was a respiratory therapist, and 1 (7%) was a medical resident. None of the confirmed case patients required hospitalization, and 21 (95%) of the 22 confirmed case patients who reported date of initial respiratory symptoms had onset after the first trainee with confirmed Ad14 infection was admitted to the hospital (Figure 1).

The attack rate by occupation among HCP who agreed to be tested is shown in Table 1. Respiratory therapists had the highest attack rate, followed by residents or fellows, nurses, medical technicians, and housekeepers. None of the attending physicians tested positive. One of the 5 unit clerks tested was positive for Ad14 infection (serologic titer for Ad14 of 1:320). This clerk worked in the intensive care unit and reported de-
veloping febrile respiratory illness after admission of a patient with Ad14.

Because misclassification of possible cases may have occurred, only confirmed Ad14 cases were included in the univariate analysis. Compared with HCP without Ad 14 infection, HCP with confirmed cases were more likely to report febrile respiratory illness (odds ratio, 8.8; \( P < .001 \)) and to have had direct contact with trainees hospitalized for Ad14 pneumonia (odds ratio, 2.8; \( P = .04 \)). We observed no statistically significant association with age, sex, underlying conditions, family member with febrile respiratory illness, coworker with febrile respiratory illness, or occupation (Table 2).

The CDC Healthcare Infection Control Practices Advisory Committee recommends that patients with adenovirus infection be placed on Droplet and Contact Precautions [23]. Of the 23 HCP with confirmed Ad14 cases who had direct contact with trainees hospitalized for Ad14 pneumonia, 12 (52%) reported that patients with Ad14 pneumonia were not in either contact or droplet precautions at the time of exposure, 10 (44%) reported that patients were in droplet and/or contact precautions at the time of exposure, and 1 (4%) did not report any information on the type of patient isolation precautions. Of the 10 confirmed cases who reported contact with patients with Ad14 pneumonia in contact and/or droplet precautions at the time of exposure, 5 said that the patient was in droplet precautions only, 1 said that patient was in contact precautions only, and 4 said that patient was in droplet and contact precautions.

**Infection control practices.** HCP infected with Ad14, as well as those who were not infected, reported similar infection control practices with regard to the use of masks, gloves, and gowns when providing care for patients with respiratory illness (Table 3). Hand hygiene practice was also similar in both groups: 90% of HCP in both groups self-reported having performed hand hygiene before and after contacting patients.

**Cohort of non-HCP.** Of the 19 non-HCP tested, 1 was identified as having a possible case of Ad14. This worker had negative PCR results but had positive results by Ad14 serology, with a titer of 1:20, and reported a cough and sore throat without fever during the survey period.

**Environmental findings.** Of the 37 hospital surfaces sampled, 7 (19%) had positive PCR results for Ad14. None of the 13 surfaces sampled in rooms from which Ad14 patients had already been discharged and terminal cleaning had been complete had positive results. One of the 12 surfaces sampled in the emergency room had positive results. This surface was the sign-in binder, where patients register for emergency room triage. Finally, 6 of the 12 surfaces sampled in the intensive care unit where 2 Ad14 patients were still hospitalized had positive results, 4 from 1 of the infected patient’s rooms (bedrail, oxygen flow machine, bedside table, and patient cabinet), 1 from the other infected patient’s room (intravenous pump touchpad), and 1 from the nursing station (computer keyboard). None of the Ad14 PCR-positive samples were found to be positive by culture.

**DISCUSSION**

The findings of this investigation support nosocomial transmission of Ad14 to HCP from infected patients. We found a higher rate of confirmed infections among HCP (13%), compared with the non-HCP control group (0%), and in the HCP group, there was an association between infection and exposure to patients with Ad14 infection. The majority (82%) of the Ad14-infected HCP reported direct contact with trainees hospitalized for Ad14 pneumonia while they were not in droplet and contact precautions. Finally, we found no associations between exposures either to other HCP or to family members with febrile respiratory illness and presence of Ad14 infection.

Our findings also raise concerns about transmission of Ad14 from HCP to patients. A high proportion of HCP with Ad14 infection reported that they continued working during the course of their acute febrile respiratory illness. According to current guidelines for preventing health care–associated pneumonia [24], HCP in acute stages of respiratory infections should be restricted from caring for high-risk patients (eg, infants and immunocompromised patients) until acute symptoms are resolved.

The Ad14 strain responsible for this outbreak among military trainees and HCP in Texas is the same strain that was responsible for civilian outbreaks in Oregon and Washington state in 2007 and a single pediatric death in New York in May 2006 [25] but distinct from the Ad14 reference strain from 1955, suggesting the emergence of a new Ad14 variant in the United States. Fortunately, in our investigation none of the Ad14-infected HCP experienced serious complications. In the Ad14 outbreak in Oregon, 1 HCP was hospitalized with severe Ad14 pneumonia that may have been acquired nosocomially; and in

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**Table 1. Attack Rate of Adenovirus Serotype 14 (Ad14) Infection by Health Care Occupation—Texas, June 2007**

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No of Ad14 infection cases</th>
<th>No of HCP tested</th>
<th>Attack rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory therapist</td>
<td>6</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Resident/fellow</td>
<td>5</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Nurses (RN/LPN)</td>
<td>14</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>Medical technician</td>
<td>5</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>Housekeeper</td>
<td>4</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Attending physician</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Clerical staff</td>
<td>1</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

**NOTE.** LPN, licensed practical nurse; RN, registered nurse; HCP, health care personnel.
the Air Force base in Texas, 3 military trainees were admitted to the intensive care unit and 1 died [22, 26]. Although precise risk factors for severe illness are unknown, extreme age, intense stress, underlying medical conditions, and high viral load may contribute to development of severe illness among Ad14-infected patients [27–29].

Outbreaks of Ad in health care settings, especially in long-term care facilities, are not unusual [14–17]; however, reports of these outbreaks tend to focus more on transmission to residents (or inpatients) rather than transmission to HCP. As shown in our investigation, transmission of Ad14 from infected hospitalized patients to HCP can occur, and rapid identification of infected HCP is needed to curtail the spread of this pathogen. Ad can spread quickly in health care settings, causing high morbidity [14, 15, 17]. Because the infecting agent is often unknown at the time that the patient is admitted to a health care facility, the CDC’s 2007 isolation precautions guidelines recommend the empirical use of transmission-based precautions according to clinical syndrome and the likely etiologic agent at the time. In military settings, Ad is a common cause of respiratory infections among trainees and should be highly suspected among trainees hospitalized with febrile respiratory illness.

### Table 2. Factors Associated with Acquisition of Adenovirus Serotype 14 (Ad14) Infection by Health Care Personnel (HCP)—Texas, June 2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCP with confirmed Ad14 infection (n = 28)</th>
<th>HCP without Ad14 infection (n = 183)</th>
<th>OR (95% CI)</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRI</td>
<td>57</td>
<td>11</td>
<td>8.8 (3.7–21.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>29 (19–57)</td>
<td>33 (18–66)</td>
<td>1.1 (0.9–1.1)</td>
<td>.1</td>
</tr>
<tr>
<td>Direct contact with Ad14-infected patients</td>
<td>82</td>
<td>62</td>
<td>2.8 (1.1–7.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>43</td>
<td>38</td>
<td>1.2 (0.5–2.6)</td>
<td>.6</td>
</tr>
<tr>
<td>Underlying condition</td>
<td>23</td>
<td>19</td>
<td>1.2 (0.5–3.0)</td>
<td>.5</td>
</tr>
<tr>
<td>Family member with FRI</td>
<td>21</td>
<td>24</td>
<td>0.9 (0.3–2.3)</td>
<td>.8</td>
</tr>
<tr>
<td>Coworker with FRI</td>
<td>7</td>
<td>15</td>
<td>2.5 (0.3–20.3)</td>
<td>.4</td>
</tr>
<tr>
<td>Nurse occupation</td>
<td>45</td>
<td>46</td>
<td>1.0 (0.5–2.3)</td>
<td>.9</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of HCP, unless otherwise indicated. CI, confidence interval; FRI, febrile respiratory illness; OR, odds ratio.

^a Univariate analysis.

### Table 3. Infection Control Practices Reported by Health Care Personnel (HCP) when Caring for Patients with Respiratory Illness—Texas, June 2007

<table>
<thead>
<tr>
<th>Personal protective equipment</th>
<th>HCP with Ad14 infection,^a % (n = 26)</th>
<th>HCP without Ad14 infection,^ab % (n = 156)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of masks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only if precaution notice was posted on patient’s door</td>
<td>69</td>
<td>58</td>
<td>.3</td>
</tr>
<tr>
<td>Always</td>
<td>12</td>
<td>12</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Sometimes</td>
<td>8</td>
<td>12</td>
<td>.7</td>
</tr>
<tr>
<td>Almost never or never</td>
<td>12</td>
<td>10</td>
<td>.7</td>
</tr>
<tr>
<td>Use of gloves</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only if precaution notice was posted on patient’s door</td>
<td>31</td>
<td>25</td>
<td>.5</td>
</tr>
<tr>
<td>Always</td>
<td>62</td>
<td>49</td>
<td>.3</td>
</tr>
<tr>
<td>Sometimes</td>
<td>8</td>
<td>13</td>
<td>.5</td>
</tr>
<tr>
<td>Almost never or never</td>
<td>0^c</td>
<td>5</td>
<td>.9</td>
</tr>
<tr>
<td>Use of gowns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only if precaution notice was posted on patient’s door</td>
<td>77</td>
<td>59</td>
<td>.08</td>
</tr>
<tr>
<td>Always</td>
<td>12</td>
<td>10</td>
<td>.7</td>
</tr>
<tr>
<td>Sometimes</td>
<td>12</td>
<td>7</td>
<td>.4</td>
</tr>
<tr>
<td>Almost never or never</td>
<td>0^c</td>
<td>16</td>
<td>.1</td>
</tr>
</tbody>
</table>

^a Limited to HCP who provide direct patient care.

^b Thirteen HCP in this group did not respond to the questions.

^c A value of .5 was given for cells with a null value.
illness. It is also recommended in the CDC’s infection control guidelines that patients with suspected viral respiratory infections be placed in contact and droplet precautions until infectious agents transmitted by both contact and droplet routes, such as adenovirus and influenza virus, are ruled out [23].

In our investigation, initial delays in placing infected patients in proper isolation precautions might have contributed to transmission from infected patients to HCP. As expected, HCP reported wearing masks and gowns only if a precaution notice was posted on the patient’s door. Contact with patients with Ad14 pneumonia was the primary risk factor in HCP who acquired Ad14 infection in this investigation, reinforcing the importance of close contact as a risk factor and the need for prompt initiation of contact and droplet precautions when adenovirus infection is suspected.

Although delays in placing the first trainees hospitalized for pneumonia in contact and droplet Precautions occurred, it is important to highlight that the hospital instituted additional control measures as soon as the outbreak in the military base was recognized to be caused by Ad and the first trainees admitted were confirmed to have Ad pneumonia. Control measures included placement of trainees with suspected Ad infection in contact and droplet precautions from the moment of arrival in the emergency room and reinforcement of hand hygiene practices. The findings of our investigation also led the hospital to enhance surveillance for febrile respiratory illness among HCP and to enhance education on infection control practices. These control measures were successful in halting further transmission.

The CDC Healthcare Infection Control Practices Advisory Committee recommends daily cleaning of frequently touched surfaces such as bed rails, carts, bedside commodes, and faucet handles in inpatient rooms housing patients with respiratory virus infections [30]. Although we were unable to isolate Ad14 from the environmental samples that were positive by PCR, 6 (86%) of the 7 PCR-positive samples came from the unit where Ad14 patients were still hospitalized, reinforcing the importance of daily cleaning of frequently touched surfaces in patient-care areas.

This study is subject to certain limitations. First, incomplete enrollment (45% of HCP agreed to be tested) makes it difficult to be certain how the findings relate to other HCP in this facility. Second, as with any survey conducted weeks to months after the event (ie, HCP exposure to Ad14-infected patients), inability to accurately recall events and exposures or bias in recall may have confounded our results. In addition, we could not confirm when infections occurred or whether reported symptoms were associated with Ad14 infection or another precipitating infection or event. Third, we may have misclassified some cases and non-cases. For example, some Ad14-neutralizing antibodies may have been induced by infection with other group-B Ads (ie, Ad7 and Ad11). Group-B Ads can induce cross-reacting neutralizing antibodies. Our cut-off value of 1:80, however, is higher than values found in any serum tested from military trainees on arrival at training [22] or our non-exposed control group and is likely strongly indicative of recent acute infection. In addition, the majority of patients with titers ≥1:80 presented clinical syndromes consistent with Ad infection, which further support the cut-off value we chose. Fourth, the long interval between environmental samples collection and processing may have impacted culture results.

In conclusion, a new genomic variant of Ad14 seems to be emerging in the US [25, 29], and transmission from infected patients to HCP can occur if existing infection control guidelines are not strictly followed. Measures to prevent transmission of Ad in health care facilities should include placing patients with suspected Ad infection or with respiratory infection of unknown etiology in contact and droplet precautions at hospital admission, cleaning environmental surfaces in patient rooms daily, and identifying and removing HCP with febrile respiratory symptoms from direct patient contact.

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