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# Acute Respiratory Disease Associated with Adenovirus Serotype 14 --- Four States, 2006--2007

Adenovirus serotype 14 (Ad14) is a rarely reported but emerging serotype of adenovirus that can cause severe and sometimes fatal respiratory illness in patients of all ages, including healthy young adults. In May 2006, an infant in New York aged 12 days died from respiratory illness caused by Ad14. During March--June 2007, a total of 140 additional cases of confirmed Ad14 respiratory illness were identified in clusters of patients in Oregon, Washington, and Texas. Fifty-three (38%) of these patients were hospitalized, including 24 (17%) who were admitted to intensive care units (ICUs); nine (5%) patients died. Ad14 isolates from all four states were identical by sequence data from the full hexon and fiber genes. However, the isolates were distinct from the Ad14 reference strain from 1955, suggesting the emergence and spread of a new Ad14 variant in the United States. No epidemiologic evidence of direct transmission linking the New York case or any of the clusters was identified. This report summarizes the investigation of these Ad14 cases by state and city health authorities, the U.S. Air Force, and CDC. State and local public health departments should be alert to the possibility of outbreaks caused by Ad14.

## New York

In May 2006, a fatal case of Ad14 illness occurred in New York City in an infant girl aged 12 days. The infant was born after a full-term pregnancy and uncomplicated delivery. She was found dead in bed, where she had been sleeping. The infant had been examined 3 days after birth and noted to have lost weight but was otherwise healthy. The next week she had decreased tears with crying, suggesting early dehydration. Physical activity and feeding progressively decreased during the week before her death.

Postmortem tracheal and gastric swabs from the infant were sent to the Wadsworth Center laboratory of the New York State Department of Health, where adenovirus was detected by polymerase chain reaction (PCR). Adenovirus also was isolated by culture, confirmed by immunofluorescence assay (IFA), and typed as Ad14 by antibody neutralization assay. Analysis at CDC identified the same unique genetic sequences in this isolate as were later identified in the Ad14 isolates from the three 2007 clusters.

Autopsy and histologic findings at the Office of the Chief Medical Examiner in New York City included presence in the lung of chronic inflammatory cells with intranuclear inclusions, consistent with adenoviral bronchiolitis and acute respiratory distress syndrome. Investigation by the New York City Department of Health and Mental Hygiene has not identified any other local cases of Ad14 illness.

## Oregon

In early April 2007, a clinician alerted the Oregon Public Health Division (OPHD) regarding multiple patients at a single hospital who had been admitted with a diagnosis of severe pneumonia during March 3--April 6. A total of 17 specimens were obtained from patients; 15 (88%) yielded isolates that were identified by CDC as Ad14. Through retrospective examination of laboratory reports from the three clinical laboratories in the state that have virology capacity and the Oregon State Public Health Laboratory (OSPHL), OPHD identified 68 persons who tested positive (by culture, PCR, or IFA) for adenovirus during November 1, 2006--April 30, 2007. Isolates from 50 (74%) of these patients were available for further adenovirus typing at either CDC or OSPHL. Of the 50 patient isolates, 31 (62%) were identified as Ad14, and 15 (30%) were identified as another adenovirus type 103.

figure); four (8%) did not test positive for adenovirus.

Among 30 Ad14 patients (i.e., all but one) whose medical charts were reviewed, 22 (73%) were male; median age was 53.4 years (range: 2 weeks–82 years). Five cases (17%) occurred in patients aged <5 years, and the remaining 25 (83%) occurred in patients aged >18 years. Twenty-two patients (73%) required hospitalization, sixteen (53%) required intensive care, and seven (23%) died, all from severe pneumonia. Median age of the patients who died was 63.6 years; five (71%) were male. One death occurred in an infant aged 1 month. Of the 30 Ad14 cases with patient residence information available, 28 (93%) occurred in residents of seven Oregon counties, and two cases occurred in residents of two Washington counties. No link was identified in hospitals or the community to explain transmission of Ad14 from one patient to another.

In comparison with the Ad14 patients, among the 12 adenovirus non-type 14 patients (i.e., all but three) whose medical charts were reviewed, nine (75%) were male. Median age was 1.1 years, and 11 (92%) patients were aged <5 years. Two (17%) adenovirus non-type 14 patients required hospitalization; no ICU admissions or deaths were reported in this group.

### Washington

On May 16, 2007, the Tacoma-Pierce County Health Department notified the Washington State Department of Health (WADOH) of four residents housed in one unit of a residential-care facility who had been hospitalized recently for pneumonia of unknown etiology. The patients were aged 40–62 years; three of the four were female. One patient had acquired immunodeficiency syndrome (AIDS); the three others had chronic obstructive pulmonary disease. All four were smokers.

The patients had initial symptoms of cough, fever, or shortness of breath during April 22–May 8, 2007. Three patients required intensive care and mechanical ventilation for severe pneumonia. After 8 days of hospitalization, one patient with AIDS died; the other patients recovered. Respiratory specimens from all four patients tested positive for adenovirus by PCR at the WADOH laboratory; isolates were available from three patients, and all three isolates were identified as Ad14 by CDC. Ad14 had last been identified in an isolate from a patient from Washington in May 2006, marking the first identification of Ad14 in the state since 2004. Active surveillance among facility residents and staff did not identify any other cases of Ad14 illness.

### Texas

Since February 2007, an outbreak of cases of febrile respiratory infection\* associated with adenovirus infection has been reported among basic military trainees at Lackland Air Force Base (LAFB). During an initial investigation, conducted from February 3 to June 23, out of 423 respiratory specimens collected and tested, 268 (63%) tested positive for adenovirus; 118 (44%) of the 268 were serotyped, and 106 (90%) of those serotyped were Ad14. Before this outbreak, the only identification of an Ad14 isolate at LAFB occurred in May 2006 (1).

During February 3–June 23, 2007, a total of 27 patients were hospitalized with pneumonia (median hospitalization: 3 days), including five who required admission to the ICU. One ICU patient required extracorporeal membrane oxygenation for approximately 3 weeks and ultimately died. All 16 hospitalized patients from whom throat swabs were collected, including the five patients admitted to the ICU, tested positive for Ad14. Fifteen of these hospitalized patients tested negative for other respiratory pathogens, and one patient had a sputum culture that was positive for *Haemophilus influenzae*.

All health-care workers from hospital units where trainees had been admitted were offered testing for Ad14, regardless of history of respiratory illness. Of 218 health-care workers tested by PCR, six (3%) were positive for Ad14; five of the six reported direct contact with hospitalized Ad14 patients.

Prevention measures implemented during the outbreak included increasing the number of hand-sanitizing stations, widespread sanitizing of surfaces and equipment with appropriate disinfectants, increasing awareness of Ad14 among trainees and staff members, and taking contact and droplet precautions for hospitalized patients with Ad14. Beginning on May 26, trainees with febrile respiratory illness were confined to one dormitory and both patients and staff members were required to wear surgical masks.

**Cases reported postinvestigation.** Since the investigation, new cases of febrile respiratory illness have continued to occur at LAFB, but the weekly incidence has declined from a peak of 74 cases with onset during the week of May 27–June 2, to 55 cases with onset during the week of September 23–29 (the most recent period for which data were available). In addition, during March–September 2007, three other military bases in Texas that received trainees from LAFB reported a total of 220 cases of Ad14 illness (Air Force Institute for Operational Health, personal communication, 2007). However, whether Ad14 spread from LAFB to these three bases has not been determined. Ad14 also was detected in April in an eye culture from an outpatient in the surrounding community who had respiratory symptoms and conjunctivitis. No link between this case and the LAFB cases was identified.

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### Editorial Note:

Adenoviruses were first described in the 1950s and are associated with a broad spectrum of clinical illness, including conjunctivitis, febrile upper respiratory illness, pneumonia, and gastrointestinal disease. Severe illness can occur in newborn or elderly patients or in patients with underlying medical conditions but is generally not life-threatening in otherwise healthy adults. Adenoviruses are known to cause outbreaks of disease, including keratoconjunctivitis, and tracheobronchitis and other respiratory diseases among military recruits (2,3). Although adenovirus outbreaks in military recruits are well-recognized (3), infection usually does not require hospitalization and rarely requires admission to an ICU. Beyond the neonatal period, deaths associated with community-acquired adenovirus infection in persons who are not immunodeficient are uncommon and usually sporadic.

Fifty-one adenovirus serotypes have been identified (4). The cases described in this report are unusual because they suggest the emergence of a new and virulent Ad14 variant that has spread within the United States. Ad14 infection was described initially in 1955 (5) and was associated with epidemic acute respiratory disease in military recruits in Europe in 1969 (6) but has since been detected infrequently. For example, during 2001–2002, Ad14 was associated with approximately 8% of respiratory adenoviral infections in the pediatric ward of a Taiwan hospital, with approximately 40% of Ad14 cases in children aged 4–8 years manifesting as lower airway disease (7).

The National Surveillance for Emerging Adenovirus Infections system includes military and civilian laboratories at 15 sites. During 2004–2007, this surveillance system detected 17 isolates of Ad14 from seven sites (8). Ten of the 17 isolates (60%) were collected from three military bases (8). Despite this surveillance, adenovirus infections often go undetected, because few laboratories routinely test for adenovirus and even fewer do serotyping. Wider circulation of Ad14 might have occurred in recent years and might still be occurring.

Further work is needed to understand the natural history of Ad14, risk factors for severe Ad14 disease, and how Ad14 transmission can be prevented effectively. Vaccines against adenovirus serotypes four and seven (i.e., Ad4 and Ad7) were used among military recruits during 1971–1999, before vaccines were no longer available. Adenoviral disease among U.S. military recruits subsequently increased (9). Ad4 and Ad7 oral vaccines have been redeveloped and are being evaluated in clinical trials. Work is ongoing to determine whether the new Ad4 and Ad7 vaccines will protect against Ad14 infection. Management of adenoviral infections is largely supportive. A number of antiviral drugs, including ribavirin, vidarabine, and cidofovir, have been used to treat adenoviral infections such as Ad14, but none have shown definitive efficacy against adenoviruses (2).

Control of adenovirus outbreaks can be challenging because these viruses can be shed in both respiratory secretions and feces and can persist for weeks on environmental surfaces. Guidelines for the care of patients with pneumonia (10) should be followed in cases of suspected adenoviral pneumonia.

Clinicians with questions related to testing of patients for adenovirus or Ad14 infection should contact their state health departments, which can provide assistance. State health departments and military facilities should contact CDC to report unusual clusters of severe adenoviral disease or cases of Ad14 or to obtain additional information

regarding laboratory testing.

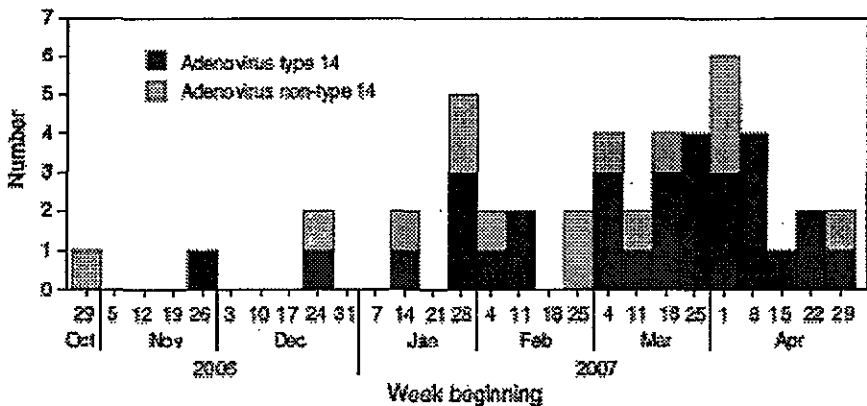
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Defined as 1) fever  $\geq 100.5^{\circ}\text{F}$  ( $\geq 38.1^{\circ}\text{C}$ ) plus at least one other sign or symptom of respiratory illness or 2) diagnosis of pneumonia.

Figure

FIGURE. Number of cases of laboratory-confirmed adenovirus (type 14 and non-type 14\*), by week of illness onset — Oregon, November 1, 2006–April 30, 2007



\* Confirmatory typing performed at Oregon State Public Health Laboratory or CDC.

[return to top.](#)

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日 2008年1月29日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①～③人血清アルブミン④人血液凝固第XIII因子 ⑤⑥フィブリノゲン加第XIII因子			Clinical outcome of frequent exposure to Torque Teno virus (TTV) through blood transfusion in thalassemia patients with or without hepatitis C virus (HCV) infection	公表国 米国	
販売名(企業名)	①アルブミン-ベアリング②アルブミン-5% ③アルブミン-25%④フィプロガミン P⑤ベリプラスト⑥ベリプラストP コンビセット (CSL ベアリング株式会社)		研究報告の公表状況	Journal of Medical Virology 1, 2008, 80/2 (365-371)		
研究報告の概要	<p>問題点(サラセミア患者の輸血による TTV 感染)</p> <p>サラセミア患者は、頻繁にウイルスに暴露された輸血に依存して肝不全や肝障害を頻繁に合併している。HBV と HCV 検査によるスクリーニング導入以来、この患者グループでの輸血関連の肝炎は激減した。しかしながら既知の肝炎に感染していないサラセミア患者の 37% がいまだに ALT 異常値を示しているが、原因は特定できていない。</p> <p>TTV は一般の人々の間で高率で広く分布しているが、特にサラセミア患者などの頻繁に輸血を受ける患者では 80%以上が複数の TTV の遺伝子型を保有している。</p> <p>著者らはアラブ首長国連邦で定期的に輸血を受ける(年間 13-18 回)サラセミア患者 197 名の TTV の遺伝子型およびフェリチン、AST、ALT レベルを検査した。</p> <p>フェリチン、AST、ALT レベルは TTV 陽性患者群が、陰性患者群より有意に高かったが、HCV と TTV 共に感染した患者群は、TTV 単独感染患者群に比べ ALT が有意に高かった。</p> <p>TTV 陽性群において ALT 異常値率は、年齢による差はなく、年間の投与間隔や投与数に起因していないことが示唆された。</p> <p>TTV ウイルスは 27 遺伝子型から成る少なくとも 5 グループに分類される。TTV DNA を RD プライマー、TT6/7/8/9 プライマーおよび NG プライマーの 3 種を用いて増幅して、遺伝子型を解析したが、TTV 感染患者のほとんどが複数の遺伝子型を保持しているため、フェリチン、AST、ALT を上昇に関与する遺伝子を特定できなかった。</p> <p>筆者らは、TTV 感染が HCV 感染患者の肝疾患を重篤にさせるとは結論できないとしている。重篤な肝疾患の進展には TTV よりも HCV の方が重要な役割を果たしている。</p>					使用上の注意記載状況・ その他参考事項等
	報告企業の意見	今後の対応				
現在まで TTV の病原性は十分解明されていないので、当社製品の原料血漿の段階で TTV に対する検査は実施されていない。 TTV と ALT に関する CPMP の見解(Plasma-derived medicinal products : position paper on ALT testing : CPMP/BWP/385/99) は、TTV DNA 値と ALT 値との間には明確な相関関係はないことを示唆しているとしている。 TTV 検査は実施していないが、本剤の製造工程(60℃10 時間の液状加熱)で不活化されると考えられる。 今後とも情報収集に努める。			今後とも情報収集に努める所存である。			

19

