Human Adenoviruses: Old Viruses, New Challenges

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Adenovirus Outbreak Leaves 6 Children Dead at N.J. Pediatric Center

University of Maryland freshman dies from adenovirus-related illness

New Jersey officials look for answers in adenovirus outbreak

Lawmakers in New Jersey held a hearing this week to look for answers as to why 11 children died in an adenovirus outbreak.

What to know about adenovirus, the common bug blamed for children’s deaths

The common virus is blamed for a growing number of deaths at a New Jersey medical facility.

30 sickened in adenovirus outbreak in New Jersey, including some who have died
Outline

- Human adenovirus (HAdV) overview and epidemiology
- HAdV in the U.S. military
- Recent outbreaks in civilian settings, including on campus
- Treatment, prevention and control
- Summary
HAdV characteristics

- Double-stranded, non-enveloped DNA virus
- First isolated in 1953 from military recruits with acute respiratory illness
- 7 species (A-G)
- ≥ 85 genotypes
- Transmission
  - Aerosol droplets
  - Contact with contaminated fomites
  - Fecal-oral
- Hardy virus that can persist in environment
 Certain HAdV types are commonly associated with particular clinical syndromes

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>HAdV Types</th>
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<tbody>
<tr>
<td>Acute respiratory illness (ARI)</td>
<td>3, 4, 7, 14, 21, 55, 1, 2, 5, 6</td>
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<td>Gastroenteritis</td>
<td>40, 41</td>
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<td>Acute hemorrhagic cystitis</td>
<td>7, 11, 34, 35</td>
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- Disseminated disease in immunocompromised hosts
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Epidemiology and severity also differ by type

- Types 1, 2, 5, 6 globally endemic types and infect most people early in life
- Types 3, 4, 7, 14, 21 epidemic types
- Types and epidemiology can be different in severely immunocompromised populations
HAdV circulates throughout the year without a distinct seasonality.

Respiratory adenovirus PCR results reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS), July 2015-February 2019.
Circulating types can vary geographically and over time

- Emerging and re-emerging HAdV types in the United States
  - HAdV-7
    - More commonly associated with severe and fatal ARI
    - In 2014, variant 7d first detected in the United States
  - HAdV-4
    - Recent reports suggest may be an underestimated cause of ARI in civilian populations
  - HAdV-14
    - 14p1 variant, earliest U.S. case in 2003
The National Adenovirus Type Reporting System (NATRS) tracks type patterns

Distribution of human adenovirus species (HAdVs) and types, by year of specimen collection — National Adenovirus Type Reporting System, 32 U.S. states and the U.S. Virgin Islands, 2003–2016
HAdV in the U.S. military: Pre-vaccine, post-vaccine, and re-implementation
Pre-vaccine: HAdV was a major cause of febrile respiratory illness (FRI) among military recruits

- Close living quarters, physical and environmental stressors, personal hygiene and persistence of HAdV in the environment
- Substantial burden of illness and missed training time drove development of a **live, non-attenuated, oral vaccine for types 4 and 7 for military use**
- Vaccine routinely given to all incoming recruits from 1971 until production ceased in 1996
- Phase-out period 1996-1999
After vaccine no longer available, HAdV cases surged, with HAdV-4 predominant as a cause of FRI

- At least eight HAdV-associated deaths in active duty personnel during 1999-2010

Increased number of HAdV infections estimated to cost $10-26 million per year, medical care and lost recruit training time

Vaccine redevelopment with new manufacturer initiated
HAdV detections and acute respiratory illness declined dramatically after vaccine reintroduction

Adenovirus serotype distribution and acute respiratory disease (ARD) rate for all US Army initial entry training sites, by month, 2010–2014

Impacts of Resumption in Military settings

- Approximately 100-fold decrease in adenovirus infections among US military recruits
  - Preventing ~13,000 febrile respiratory illnesses a year and reducing the associated lost training time and healthcare costs
- Currently, all incoming military recruits are routinely vaccinated against AdV types 4 and 7

Outbreak of Acute Respiratory Illness associated with Adenovirus Type 4 at the United States Naval Academy, 2016


Outbreak of Respiratory Illness Associated With Human Adenovirus Type 7 Among Persons Attending Officer Candidates School, Quantico, Virginia, 2017

Bautista-Gogel J, Madsen CM, Lu X, Sakthivel SK, Froh I, Kamau E, Gerber SI, Watson JT, Cooper SS, Schneider E
Recent outbreaks in U.S. civilian settings
Outbreaks on several college campuses were recognized during Fall 2018.

THE BALTIMORE SUN
What are adenoviruses, the type of pathogen that killed a University of Maryland freshman?
Literature describing civilian college outbreaks is limited

- 3 Emerging Infectious Diseases Journal reports published 2017-2018
    - 13 (8%) of 168 positive for HAdV
      - type 4 (n=8), type 14 (n=3), type 2 (n=1), type 4 & 14 (n=1)
    - 27 HAdV-4 cases from students enrolled at 7 colleges
  - PA: ILI surveillance at a single student health center site, 2016-2017
    - 44 (15%) of 288 tested positive for HAdV
      - type 3 (n=21), type 7 (n=16), type 4 (n=5), type 1 (n=2)

Lamson DM. et al. 2017; Kajon AE. et al. 2018; Biggs HM, et al. 2018
Outbreaks of HAdV-7 and -3 occurred at pediatric long-term care facilities in New Jersey, 2018

- **Facility A**
  - HAdV-7
  - 36 confirmed cases
    - 35 resident, 1 staff
    - 30 hospitalizations
    - 11 deaths
      - 10 confirmed HAdV
      - 1 suspect
  - 10 confirmed HAdV
  - 1 suspect

- **Facility B**
  - HAdV-3
  - 13 confirmed cases
    - 2 hospitalizations
    - 0 deaths

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11th child dies in adenovirus outbreak in New Jersey

By Michael Newelman, CNN

Updated 2:00 PM ET, Mon November 19, 2018
Notes from the Field: Fatalities Associated with Human Adenovirus Type 7 at a Substance Abuse Rehabilitation Facility – New Jersey, 2017

- Substance abuse rehabilitation facility outbreak
  - 4 hospitalized, 3 deaths
- College students
  - 7 cases at one college, no hospitalizations or deaths
- Sporadic community cases
  - 2 deaths
In addition to outbreaks, sporadic cases of severe HAdV illness and deaths occur, including among healthy individuals.

Treatment, Prevention, Control
No antivirals FDA-approved for the treatment of HAdV

- Cidofovir
  - Limited data (case reports, non-randomized small studies) in severely immunosuppressed patients

- Brincidofovir
  - Investigational agent for treatment of HAdV infection in immunosuppressed populations
  - Lower potential for nephrotoxicity compared to cidofovir
HAdV vaccine is licensed for use only in the military

- Lack of data to guide use in populations outside the military
- Opportunities to assess recent new applications in the military (U.S. Naval Academy and Quantico OCS)
- Important considerations and questions
  - Establishing HAdV burden of illness in civilian settings
  - Risk vs. benefit of existing live, non-attenuated vaccine in civilian populations
  - Need for development of new vaccine constructs
- No formal discussion of expanding use of vaccine currently
Vaccine precautions (package insert):

- Safety and effectiveness have not been evaluated in persons with primary or acquired immunodeficiency states.
- Vaccinees, and individuals who come in close contact with vaccinees, may be exposed to the vaccine viruses shed in the stool for up to 28 days.
- Vaccinees should exercise caution when in close contact with children less than 7 years of age, immunocompromised individuals and pregnant women during the 28 days following vaccination.

FDA, Package Insert - Adenovirus Type 4 and Type 7 Vaccine, Live, Oral
HAdV is a hardy virus that can remain infectious on environmental surfaces for long periods

- Not killed by many common disinfectants
- Special attention to use of appropriate disinfectants and cleaning of surfaces and medical equipment is important in addition to usual respiratory virus outbreak control measures
- Nosocomial outbreaks have been linked to contaminated medical equipment
- Live virus has been isolated from healthcare settings and military barracks (pillows, lockers, rifles)
HAdV Testing in Student Health Centers: Contextual Factors to Consider

- Weekly monitoring of ILI is important, with particular attention to influenza negative respiratory illness
- Clustering of ILI among a defined group (e.g., similar residence, activities, clubs, etc.) should prompt investigation
- Targeted testing, as part of clinical workup
  - Severe or hospitalized cases, immunosuppressed, comorbidities
- HAdV typing does not typically impact clinical management
  - useful to help characterize outbreaks, define clusters
Communication Challenges

- HAdVs are not new
- HAdVs are continuously present and circulating in the community
- Better testing availability has led to more recognition
  - Deaths are now able to be directly attributed to HAdVs
- Most infections are mild/asymptomatic ("cold virus")
  - But: occasional severe illness, death
- No specific treatment is recommended; supportive care only
- Preventive messaging is general: Hand/Respiratory hygiene, etc.
Summary Considerations

- HAdVs are ubiquitous with year-round community circulation;
- Sporadic cases, sometimes severe, regularly occur;
- Detections have risen with increased availability of testing;
- Some HAdV types are associated with more severe illness and occasional deaths;
- Military recruits are at high risk and routinely vaccinated for types 4 and 7; vaccination is expanding to other populations within the military;
- Risk in other congregate settings, e.g., university campuses, is unknown; more study is needed to quantify risk in these populations.
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.