Adenovirus Infections in Children

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Pediatric Pearls Conference
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Disclosure

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- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
adenovirus
Objectives

• Clinical Manifestations in Children
  – Immunocompetent
  – Immunocompromised
• Diagnostics for Adenovirus
• Vaccine in military
• Adenovirus as a vector
Human Adenoviruses (HAdV)

- Animal adenoviruses: *Mastadenovirus* (mammals), Aviadenovirus (birds), fish, and Human Adenovirus (type of Mastadenovirus)
- First isolated from adenoid tissue
- "Adeno" means "gland" in Greek
- Discovered in 1953
Respiratory virus jumps from monkeys to humans

Adenovirus remained infectious after crossing species barrier.

Zoe Cormier

A class of virus has for the first time been shown to jump from animals to humans — and then to infect other humans.

The virus is described in *PLoS Pathogens* today. The team that discovered it might also have found the first human to be infected: the primary carer for a colony of titi monkeys (*Callicebus cupreus*) that suffered an outbreak.
Adenovirus: History

- 22 y/o lab technician accidentally sprayed fluid with HAdV 22 into her eye and washed eye immediately
- 7d later, itching, watery eye and redness, foreign body sensation
- Peak of illness D14, follicles in upper and lower conjunctiva
- Ceased by D21, no fever.

Sever, NEJM 1962
Human Adenoviruses (HAdV): History

- **1960s**: Volunteers: epidemic keratoconjunctivitis
- **Historical records**: similar types of epidemics that are thought to be due to HAdV
- Hemorrhagic cystitis, hepatitis, gastroenteritis, and myocarditis
- Incubation period 2-14 days
Human Adenovirus (HAdV)

- Human adenoviruses:
  - DNA virus
  - Six species: A, B, C, D, E, F, G
  - Hexon, fiber, and penton genes.
  - >50 types
Epidemiologic Peak of Adenovirus

Peak age/incidence between 6 mo-5yrs
Species of Adenovirus
<table>
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<tr>
<th>Type</th>
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<td>3, 7, 14</td>
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<td></td>
<td>1,2,5</td>
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<td>40</td>
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</table>
Diagnosis of Adenovirus

• Viral culture (historic)
• Direct immunofluorescence
• For diarrhea, generally think about serotypes 40/41 (species F)
  – Antigen based detection
• PCR based diagnosis
  – Highly sensitive
  – Known to shed for months after an infection
  – Persistence in tonsils/adenoids
HAdV and the Upper Resp Tract

- 5 yo female with 5 days of fever, to 104. She complains of sore throat and dysphagia. Exudative tonsillitis noted at PCP office. Rapid strep/culture negative.
- 1d PTA, developed rhinorrhea. Also complains of lower abdominal pain and headache.
- Went to OSH 7/22 for worsening symptoms, and got a chest Xray, IV fluids, and CT scan which showed minimal amount of fluid around the gallbladder.
- Exam: Exudative tonsillitis. Left sided abdominal pain
Adenovirus and Upper Resp Tract

- Non-specific URI
- Otitis media
- Exudative tonsillitis/pharyngitis*
- Pharyngoconjunctival fever
- Pertussis-like syndrome
- Fever (96%), malaise, abdominal pain
- Elevated CRP and WBC count

*Dominguez, O 2005 PIDJ
Adenovirus and the Eye

- **Acute conjunctivitis**
  - Watery eye/crusting, foreign body sensation, starts unilaterally, follicles in the inferior palpebral

- **Kerato-conjunctivitis**
  - Painful corneal opacities, pre-auricular lymphadenopathy, protracted illness, HAdV D

- **Pharyngoconjunctival fever** (fever, follicular conjunctivitis and cervical/preauricular adenitis). Outbreaks associated with unchlorinated water exposure

- **Mimics peri-orbital/orbital cellulitis**
PHARYNGOCONJUNCTIVAL FEVER

EPIDEMIOLOGICAL STUDIES OF A RECENTLY RECOGNIZED DISEASE ENTITY

Joseph A. Bell, M.D., Wallace P. Rowe, M.D., Joseph I. Engler, M.D., Robert H. Parrott, M.D.

• “The fever not uncommonly spiked to 103 or 104 F, lasted from 1 to 10 days (the median was 5 to 6 days), and was often the chief complaint”.
• The sore throat was generally quite mild and was described more as a discomfort or scratchiness. Examination generally showed nothing striking except that the posterior oral pharynx was frequently injected and prominently studded with glary lymph follicles.
• Conjunctivitis lasting a few days to three weeks was manifest by injection of both the bulbar and palpebral conjunctivas. The conjunctivitis was of the mild follicular type, frequently monocular.
• Nontender, preauricular lymphadenopathy was occasionally noted.
• A purulent exudate was almost nonexistent, but a scanty, serous exudate, with some slight matting together of the eyelids and excessive lacrimation, was not uncommon.

JAMA, 1955
Follicular conjunctivitis

Keratitis
• 7-month-old boy with severe edema and erythema of the right upper and lower eyelids
• A pseudomembrane was present on the palpebral conjunctiva
• Adenovirus type 8 grew in conjunctival culture.
(HAdV)—associated epidemic keratoconjunctivitis (EKC) outbreaks —2008–2010

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<th>Minnesota</th>
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<td>2009</td>
<td>2008</td>
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<td>NICU</td>
<td>Clinic</td>
<td>Clinic</td>
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<tr>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total EKC cases</td>
<td>37</td>
<td>18</td>
<td>70</td>
<td>286</td>
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<tr>
<td>HAdV serotype identified</td>
<td>HAdV-8</td>
<td>HAdV-19</td>
<td>HAdV-8</td>
<td>HAdV-8, HAdV-3*</td>
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<tr>
<td>Infection control breach at facility</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>HAdV detected on medical equipment</td>
<td>Not tested</td>
<td>Yes</td>
<td>Not tested</td>
<td>Yes (in 1 of 3 outbreaks)</td>
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</table>

MMWR, August, 2013
Infection Prevention: Office Setting

• Strict adherence to hand hygiene among staff members
• Use of disposable gloves for any potential contact with eye secretions
• Disinfection of ophthalmic instruments after each use (or use of disposable equipment)
• Cohorting of suspected conjunctivitis patients (separate waiting room, sign-in area, and examination room)
• Furloughing of staff members who have signs and symptoms consistent with EKC.
• Dedicating eye drop vials to single patients
HAdV and Lower Respiratory Tract Illness
NCH Case: Severe Resp Distress

• A 17-year-old male with 4d of sore throat, cough, and fever. Had hypoxia, ↑HR/RR, crackles on exam

• At NCH, he was placed on 2L O2 NC. CXR/chest CT scan showed multifocal tree in bud, micronodular, and macronodular pattern with bilateral mediastinal and hilar lymphadenopathy. Negative studies included: urine histoplama antigen, AFB/fungal cultures, urine legionella.

• HD4, he developed hypotension and required intubation.

• Respiratory panel + for HAdV from NP, BAL and blood HAdV+. All other studies negative.

• Patient discharged on HD 13.
<table>
<thead>
<tr>
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<th>C</th>
<th>D</th>
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<td></td>
<td>x</td>
<td>x</td>
<td>1,2,5</td>
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</table>

Peak age/incidence between 6 mo-5yrs
Severe Serotype 14 Infection

• 2006, NY: Fatal case, aged 12 days (former FT, uncomplicated delivery). She was found dead in her crib.

• Adenovirus also was isolated by culture, confirmed by immunofluorescence assay (IFA), and typed as Ad14 by antibody neutralization assay from resp secretions.

• Presence in the lung of chronic inflammatory cells with intranuclear inclusions, consistent with adenoviral bronchiolitis

• Outbreaks in long term care facilities, military trainees

MMWR, 2007
A. Serotype distribution

- **Total number**
- **Death number**

Case number:

- **Type 2**
- **Type 3**
- **Type 7**


[Link to the article](http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0053614)
Adenovirus in the Military

• Severe disease in military recruits (basic training) reported since 1960s*
• Lymphopenia reported*
• A vaccine against adenovirus types 4 and 7 was given to U.S. military recruits from 1971 to 1999

FATAL PNEUMONIA ASSOCIATED WITH ADENOVIRUS TYPE 7 IN THREE MILITARY TRAINEES

Burton A. Dudding, M.D., Stanley C. Wagner, M.D., Jack A. Zeller, M.D., John T. Gmelich, M.D., George R. French, Ph.D., and Franklin H. Top, Jr., M.D.

NEJM, 1972
## LRTI and the Military

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Branch</th>
<th>Age, y/sex</th>
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<td>Illinois</td>
<td>Navy</td>
<td>18/M</td>
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<td>ND</td>
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<td>2003</td>
<td>Missouri</td>
<td>Army</td>
<td>21/M</td>
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<td>2003</td>
<td>Oklahoma</td>
<td>Army</td>
<td>18/M</td>
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<td>4, 7</td>
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<td>2003</td>
<td>California</td>
<td>Marine Corps</td>
<td>32/M</td>
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<td>2004</td>
<td>Oklahoma</td>
<td>Army</td>
<td>22/M</td>
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<td>2007</td>
<td>Texas</td>
<td>Air Force</td>
<td>19/F</td>
<td>Yes</td>
<td>14</td>
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<td>2009</td>
<td>Texas</td>
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<td>19/M</td>
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</table>

New live, oral vaccine for types 4 and 7 was approved by FDA March 2011 (17-50 years)

Potter, Emerging Infectious Diseases 2012
Acute Hemorrhagic Cystitis

- Most often in boys
  - Japan, type 11 or 21
- Usually no fever or hypertension
- Can be confused with glomerulonephritis
- Renal transplant, HSCT, or other immunocompromised host

Numazaki NEJM 1968
Gastroenteritis

- 7.2% of infantile diarrhea, Species A and F (40/41) – 8-12 days of symptoms
- Adenoviruses may be excreted in feces for months after a primary infection.
- Intussusception Associated With Adenovirus
- ICH: Adenovirus 5 associated with hepatitis and variety of types associated with diarrhea

Uhnoo J Clin Micro 1984
Partially necrotic segment of terminal ileum, which showed mural edema and focal hemorrhagic necrosis.

**Intussusception Associated With Adenovirus.**
Arbizu, Ricardo; Aljomah, Ghanim; Kozielski, Rafal; Baker, Susan; Baker, Robert

*Journal of Pediatric Gastroenterology & Nutrition.*
DOI: 10.1097/MPG.0b013e3182868971
High-power view showing intranuclear inclusions (arrows)

Intussusception Associated With Adenovirus. Arbizu, Ricardo; Aljomah, Ghanim; Kozielski, Rafal; Baker, Susan; Baker, Robert

DOI: 10.1097/MPG.0b013e3182868971
Immunohistochemistry: + for HAdV

Intussusception Associated With Adenovirus.
Arbizu, Ricardo; Aljomah, Ghanim; Kozielski, Rafal; Baker, Susan; Baker, Robert

DOI: 10.1097/MPG.0b013e3182868971
HAdV in the neonate

- 26 infants identified over a 17 year period
- Respiratory disease, temperature instability. Disseminated disease in 5 children (four of whom died).
- Neonates less than 14 days of age were more likely to have disseminated disease
- Vertical transmission of HAdV
- Horizontal transmission of HAdV

Ronchi, A J, Sanchez P. Pediatrics
Adenovirus: Infection Control

- Respiratory droplet, fecal/oral, vertical transmission
- Contaminated fomites can survive for up to 35 days on inanimate surfaces.
- Nosocomial transmission has been documented
- Hospital workers with conjunctivitis should avoid patient care for 14 days
How do I know if a child with identified HAdV really has acute disease or it is just incidental detection?

Detection rate from NP swabs: culture: 0.6%
Detection rate from NP swabs: PCR: 11%

Detection does NOT necessarily equate disease
All species but especially Species C can be incidentally detected!

- Children with resected tonsils and adenoid tissue (n=203)
- The presence of viral DNA peaked at 4 years of age and declined thereafter
- All species C serotypes were represented in these tissues.
- Infectious virus was detected infrequently
- Species C adenoviruses can establish latent infections in mucosal lymphocytes

Garnett, J Virology 2009
<table>
<thead>
<tr>
<th>Age(month)/Sex</th>
<th>Clinical Phenotype</th>
<th>HAdV Cts</th>
<th>HAdV Species</th>
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<td>55.4/F</td>
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<td>37.4</td>
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<td>53/M</td>
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<td>57/M</td>
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<td>F</td>
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<td>13.7/F</td>
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<td>34.2</td>
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<td>106.9/F</td>
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<td>29.6</td>
<td>C</td>
<td>S. pneumoniae</td>
<td>Pleural fluid</td>
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</tbody>
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4.5% Bacterial co-infection  
3.1% with purulent bacteria

Song et al. PIDJ 2016
<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
<th>n</th>
<th>HAdV</th>
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<td>J-Villegas</td>
<td>DFA/VC</td>
<td>251</td>
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<td>Texas</td>
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<tr>
<td>Leuin</td>
<td>DFA</td>
<td>59</td>
<td>3.4%</td>
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<tr>
<td>Chang</td>
<td>VC/PCR</td>
<td>226</td>
<td>7.5%</td>
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<tr>
<td>Taiwan</td>
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<td>Dominguez</td>
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<td>192</td>
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<td>Colorado</td>
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<td>Kim</td>
<td>Multi PCR (HBoV/CV)</td>
<td>55</td>
<td>7.3%</td>
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<td>Shike</td>
<td>Viral culture;PCR</td>
<td>70</td>
<td>2.8%, 1 additional patient by PCR</td>
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<td>California</td>
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<tr>
<td>Jaggi</td>
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<td>51</td>
<td>8.8%</td>
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<td>Ohio</td>
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Adenovirus vs. Kawasaki Disease

- Peak age under age 5
- Conjunctivitis
- Rash
- Lymphadenopathy
- Prolonged fever, high inflammatory markers
  - CRP 5.98 mg/dL, ESR 40 mm/hr
- Hepatitis

Tabain et al, PIDJ 2012
Adenovirus vs. Kawasaki Disease

- Usually begins unilaterally
- Watery or pus discharge
- Scleral hemorrhage/Cornea
- Blurry vision, foreign body sensation
- Photophobia uncommon
- Preauricular lymph node

- Bilateral
- Non-exudative
- Bulbar >tarsal
- Spares the limbus
- Iridocyclitis or anterior uveitis
Clinical Characteristics of HAdV with KD-like symptoms: 62 Subjects

- 89% had less than 4 clinical features of KD
- More common: 73% conjunctivitis, 65% with mucosal, 52% rash
- Less common: 15% with extremity, 13% node
- Median duration of fever on evaluation: 5 (5-7) days

<table>
<thead>
<tr>
<th></th>
<th>Complete KD n=10</th>
<th>HAdV Disease n=51</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESR: &gt;40mm/h</strong></td>
<td>7 (70%)</td>
<td>29 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CRP (mg/dL), Median, IQR</strong></td>
<td>8.1(4.4-20)</td>
<td>3.6 (2.1-5.7)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Platelet: cell/mm, Median, IQR</strong></td>
<td>290 (245-441)</td>
<td>260 (225-312)</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Albumin: &lt;3.0g/dl</strong></td>
<td>1 (10%)</td>
<td>3 (6%)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>ALT: &gt;45 IU/L</strong></td>
<td>7 (70%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pyuria: &gt;10/HPF</strong></td>
<td>6 (60%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Song, IDSA 2015 and Jaggi, CID 2013
<table>
<thead>
<tr>
<th></th>
<th>Complete KD n=10</th>
<th>Incomplete KD n=6</th>
<th>KD-like Acute HAdV Disease n=51</th>
<th>*p 1</th>
<th>^p 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdV threshold cycle (Ct), median, IQR</td>
<td>36.8 (25.2-38.5)</td>
<td>33.8 (21.6-39.6)</td>
<td>25.3 (21.9-29.4)</td>
<td>0.019</td>
<td>0.029</td>
</tr>
<tr>
<td>Species</td>
<td>5C (63%)</td>
<td>2C (50%)</td>
<td>8C (25%)</td>
<td>0.030</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2B (25%)</td>
<td>1B (25%)</td>
<td>21B (66%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 NT (13%)</td>
<td>1 NT (25%)</td>
<td>3E (9%)</td>
<td></td>
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</tr>
</tbody>
</table>

Lower the Ct value, higher viral burden
Species identification and viral burden may be helpful to differentiate acute HAdV disease from Kawasaki disease with incidental Adenovirus detection
Stay tuned...not ready yet for clinical use!
Other Adenovirus manifestations

• Myocarditis
  – Identified in myocardial tissue from biopsy

• Hepatitis
  – Immunocompetent hosts
  – Pediatric liver transplant patients,
  – Serotypes 1–3, 5, and 7 (most by serotype 5)
  – Rates of hepatitis range from 3% to 10% and frequently lead to graft loss and high mortality rates (up to 53%)

• Meningoencephalitis
  – Immunocompromised/immunocompetent hosts
HAdV in immunocompromised

- Reactivation of viral reservoirs vs. primary infection
- Severe LRTI, colitis, hepatitis, hemorrhagic cystitis, nephritis, encephalitis, and disseminated disease
- Asymptomatic infection vs. Disease
- Adenovirus in solid organ transplant recipients
  - Been reported as transmitted from allograft causing fatal disease (liver and kidney)

De Mezerville Pediatr Infect Dis J. 2006
Drug options

• Cidofovir
  – Nucleotide analogue, inhibits DNA polymerase
  – Approved for CMV retinitis in HIV/AIDS
  – Used for Adenovirus infections
• Nephrotoxicity, neutropenia, possibly teratogenic/carcinogenic
• Brincidofovir (CMX001)
Clinical Trial: Brincidofovir

- A Phase 3, Open-Label, Multicenter Study of the Safety and Efficacy of Brincidofovir (CMX001) in the Treatment of Early Versus Late Adenovirus Infection (NCT02087306)
- A Randomized, Placebo-Controlled Multi-Site Phase 2 Study Evaluation the Safety and Efficacy of Preemptive Treatment With CMX001 for the Prevention of Adenovirus Disease Following Hematopoietic Stem Cell Transplantation in Adults and Children (NCT01241344)

Biol Blood Marrow Transplant. 2012
Adenovirus as a Vector

• HAdV can persist in some human cell types without causing cell lysis
  – Tonsillar tissues
  – Subsets of B and T cells
• Since 1993, 400 clinical protocols
• Can infect dividing and non-dividing cells
• Prepared in large quantities in tissue culture.
A Monovalent Chimpanzee Adenovirus Ebola Vaccine — Preliminary Report
Tommy Rampling, M.R.C.P., Katie Ewer, Ph.D., Georgina Bowyer, B.A., Danny Wright, M.Sc., Egeruan B. Imoukhuede,

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B
<table>
<thead>
<tr>
<th>Type</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
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<tbody>
<tr>
<td>URI</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LRTI</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Severe LRTI</td>
<td></td>
<td></td>
<td>7,14</td>
<td></td>
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<tr>
<td>Acute conj</td>
<td></td>
<td></td>
<td>7</td>
<td>1,2,3</td>
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<td>Epidemic kerato-conj</td>
<td></td>
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<tr>
<td>Pharyngoconj. fever</td>
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<td></td>
<td>3,7</td>
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<tr>
<td>Gastroenteritis</td>
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<td>40, 41</td>
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<td>Hepatitis</td>
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<td>Hemorrhagic cystitis</td>
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<td>Myocarditis</td>
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<td>7,21</td>
<td></td>
<td></td>
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<tr>
<td>Meningoencephalitis</td>
<td></td>
<td></td>
<td>7</td>
<td>2,5</td>
<td></td>
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<tr>
<td>Disseminated disease</td>
<td>x</td>
<td>x</td>
<td>1,2,5</td>
<td></td>
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<td>40</td>
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</tbody>
</table>

Peak age/incidence between 6 mo-5yrs
Summary

• Human Adenoviruses cause a variety of clinical syndromes
• Diagnostics need to be interpreted in light of the clinical presentation
• Severe disease can occur in immunocompetent, but especially in immunocompromised children and neonates
Practice Change

• Consider adenovirus in the differential diagnosis of children with prolonged fever.
• Consider adenovirus as a cause of severe respiratory distress in children.