Case 1

16 month old with rash

- 16 month old previously “perfectly well” child
- received VZV vaccine in September 2011
- 4 healthy sibs and 2 well parents
- No animals
- No travel
- No unusual exposures:
  - No ill contacts
  - No outside caretakers
  - No daycare

Question

- 16 month old female, previously healthy, presents with elevated temperature and rash
16 month old with rash

- 2 days prior to admission: upper thighs had vesicles that dried up with bathing
- 1 day prior to admission: erupted with “vesiculobullous eruption” on arms and legs
- Day of admit
  - Admitted to hospital/ICU
  - T 40 (admission)
  - Ill and very irritable

VRDL results

- Positive Enterovirus from multiple specimen types (vesicle, throat)
  - Typed as Coxsackie A – 6 virus
Enteroviruses

- RNA viruses
- Polio and 'non-polio' viruses:
  - Group A coxsackieviruses
  - Group B coxsackieviruses
  - Echoviruses (now Parecho)
  - “numbered” enteroviruses (e.g. EV 68, EV 71)

Spread via fecal-oral and respiratory route
Most occur June-October in US

Hand-Foot and Mouth
- coxsackievirus A (especially A16) and EV71

Hand, Foot and Mouth—“classic”

Classic H, F and M
### Outbreaks enteroviruses

- Most outbreaks Hand, Foot and Mouth (HFM)
  - CV A16
  - EV 71—mostly SE Asia and Australia
  - (CVA 10 to a lesser extent)

- Sporadic cases of H, F and M associated with many of the other EV

### Significance of CAV-6?

### CAV-6-Finland

- **Finland 2008**
  - Nationwide outbreak of Hand, Foot and Mouth
  - 43 patients
  - Half were school-aged or adults: suggesting “low herd” immunity
  - Rash worse?
  - Associated with onychomadesis (periodic shedding of nails)
  - 1-2 months after acute illness
  - Nail fragments positive for CAV-6 virus
  - Some patients had neurologic complications

*Emerging Infectious Disease 2009*
CVA-6-Taiwan

- Taiwan 2010
  - Enhanced surveillance for EV because EV71
  - 130 patients positive for CVA-6
  - In addition to typical H, F and M rash
    - 66 (51%) with desquamation of palms/soles
    - 48 (37%) with onychomadesis (compared with 7 (5%) of H, F and M with non-CAV6 infection
  - Sequences of VP1 of VP1 different in Taiwan before 2010 but similar to those in Finland 2008

- BMC Infectious Diseases 2011

CVA6 Taiwan, 2010

CVA-6 in Japan

- June 2011
  - Sudden increase in H, F and M reported to National Epi
  - 709 HFMD and 156 herpangina-
    - 93 clinical samples from 108 HFMD case patients
    - 74 + CAV-6
  - Also noted neurologic disease (1 case encephalitis)

- Emerg Infect Diseases 2012

CAV6 Japan 2011 outbreak-
"typical clinical manifestations"
National data—MMWR 2012

November 7, 2011 – February 29, 2012:

- 63 persons with signs and symptoms HFMD:
  - Alabama (38)
  - California (7)
  - Connecticut (1)
  - Nevada (7)
  - Not reportable

- Of the 63 patients:
  - 40 (63%) less than 2 years
  - 15 (24%) were adult > 18 years of age
  - 44 (70%) had exposure to day care or school
  - 8 (15%) adults had contact with children in child care where HFMD had been reported

- Rash and fever more severe > “typical” HFMD
  - As well as rash on hands, feet and mouth:
    - 29 (46%) arms and legs
    - 26 (41%) face
    - 22 (35%) buttocks
    - 12 (19%) trunk
  - Shedding of nails in 2 (4%)

(N.B. most cases were relatively recent so not followed long enough)
Called “Tough new strain of H, F & M”

A few weeks after acute infection

Cases 2 & 3
Twins

...WITH DRAMATIC NEUROLOGIC PRESENTATION...SAME DAY...

Maternal course

- Mom with PROM at 21 weeks/bed rest
- Chorio-amnionitis
- Delivered 25-26 weeks gestation
- No recent travel, no ill contacts
Case 2: Twin A

- Hospital course complicated by (fairly typical premie course): prolonged bumpy course:
  - Respiratory distress syndrome
  - Chronic lung disease
  - PDA, s/p ligation
  - Grade 2 intraventricular hemorrhage
  - Retinopathy of prematurity
  - By 3 months of age: relatively stable: off vent, on supplemental O2 and on feeds (nipple feeds), and gaining weight

- ~3.5 months of age [corrected gestational age ~ ‘full term’]
  - More lethargic
  - Decreased feeding
  - Worsening apnea → required ventilatory support
- One day later
  - Seizures
  - Transferred to PICU

---

Case 2: Twin A

- Exam
  - Grossly edematous former premie, intubated
  - Afebrile
  - Hepatosplenomegaly
  - No rashes
  - Neuro: does not wake, + respond to pain, increased tone throughout

- Neuroimaging
  - Bilateral (right > left) cytotoxic edema of cerebral hemispheres in a watershed distribution. Distribution of injury c/w watershed distribution

- Lab
  - WBC 7.5 (30% P, 52% L, 3% Mo), Plt = 201,
  - CSF: WBC 2 [30% P, 50% L, 20 Mo], RBC 600
  - Blood and CSF - No growth
  - Work up for EV, CMV, HSV – neg
Case 3: Twin B

- Similar hospital course as Twin A but less sick and had been discharged home 2 weeks prior
  - Same time as sibling became ill
    - Poor feeding
    - Lethargy and
    - Seizures
  - Admitted to hospital for work-up and treatment

- Exam: tone normal, does open eyes spontaneously, interactive
- LABs
  - WBC 6.1 (32% P, 50% L, 50% Mo)
  - CSF 1 WBC, 0 RBCs, G 65, Pr 45
  - Blood/CSF cultures negative
  - HSV, EV, adenov, flu, rotavirus w/u negative
- MRI: bilateral white matter disease

Case 2 and 3: Twins

1. A. Botulism
2. B. Enterovirus
3. C. Parechovirus
4. D. E coli sepsis
5. E. Influenza H1N1

<table>
<thead>
<tr>
<th>Case 2 and 3: Twins</th>
<th>Parechovirus PCR testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A. Botulism</td>
<td>Both became ill same day, specimens for Parecho testing submitted 8 days later (* for Twin B’s serum specimen/date not sure)</td>
</tr>
<tr>
<td>2. B. Enterovirus</td>
<td></td>
</tr>
<tr>
<td>3. C. Parechovirus</td>
<td></td>
</tr>
<tr>
<td>4. D. E coli sepsis</td>
<td></td>
</tr>
<tr>
<td>5. E. Influenza H1N1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>Serum</th>
<th>Respiratory</th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin A (ICU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin B (home)</td>
<td></td>
<td>*</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
### Parechoviruses

- **Human Parecho**
  - Many formerly enterovirus (e.g. Echo 22, Echo 23)

- **Clinically**
  - < 2 years of age
  - PCR for EV does not detect this virus so would have missed the virus

### Parecho and neonatal infections

- **HPeV (especially type 3)**
  - Important cause of severe infections in very young children
    - Sepsis, encephalitis and hepatitis
    - Clinical manifestation overlap with EV and bacterial sepsis
    - Only ~10-15% of patients neonatal sepsis with bacterial causes-
      - Remainder presumed to be viral

### Parecho and neonatal infections

- HPeV encephalitis, of 10 cases:
  - Similar to enterovirus
  - Most frequently: fever, seizures, irritability, rash and feeding problems
  - Seizures and periventricular white matter
  - Neurodevelopmental outcome; Only 1 of 10 with pleocytosis (similar to the cases here)
    - Cerebral palsy (1)
    - Learning disability (1)
    - Epilepsy (1)
    - Developmental abnormalities (1)
    - Normal (6)

  - Verboon-Maciulek, Ped Inf Dis J 2008

### Case 4
Case 4

- 3 week old, previously healthy, Hispanic female presented to healthcare provider with fussiness
- Household members with cough illness
- Lived with mother, father, 3 siblings, uncles, aunts, and 2 cousins
- Symptom onset age 3 weeks
- Seen by healthcare provider 3 times in 3 days prior to admit
- PMH: Full-term, uncomplicated pregnancy

Case 4

- Seen in ER and Admitted (3 day history of low-grade fever, cough, and respiratory distress)
- Transferred from community hospital to children's hospital PICU for intubation
- WBC 47,500; 65% lymphocytes
- Diagnostic studies were sent...

What is the most likely diagnosis?

1. A. RSV
2. B. Influenza
3. C. Human metapneumovirus
4. D. Measles
5. E. Herpes simplex
6. F. Pertussis

Pertussis
**Background**

- **Bordetella pertussis**: gram negative, fastidious, pleomorphic bacillus
- ‘whooping’ cough
- “100” day cough
- Highly infectious (during catarrhal phase and 1st 2 weeks of cough)

**Epidemiology**

- Prior to vaccine, >200,000 cases/year, used to be most common childhood illness
- Still major problem in developing countries, (among the 10 leading causes of childhood mortality)
- Outbreaks in the US have “ballooned” in regions across the US “breaking records”
U.S. Pertussis Cases: 1922-2011*

Only vaccine-preventable disease in the US increasing...

changes in pertussis reporting by state from 2011 to 2012*

CDC website:
Europe also experiencing increase

### Clinical (outside neonatal period)

- 3 stages: catarrhal, paroxysmal, and convalescence
- Classical presentation
  - coryza; no pharyngitis
  - paroxysmal cough, posttussive vomiting & "whoop"
  - no systemic illness, no fever, no pharyngitis
- Cough often quite prolonged and severe
- Adults with pertussis often report sweating episodes and feeling as if they're choking on something

### Stages of Disease in Weeks

- Symptom Onset
- Incubation Period
- Catarrhal Stage
- Paroxysmal Stage
- Convalescent Stage
- Communicable Period

### Child with broken blood vessels in eyes, bruising on face (9th cough)
Pertussis in Young Infants (< 6 month)

- Infant initially looks deceptively well; coryza, no or minimal fever, mild or no apparent cough
- Later:
  - Gagging, gasping
  - Bradycardia or Apneic episodes
  - Cyanosis (parents may report red or purple face)
  - Post-tussive emesis

Complications in infants

- Infants can develop very high lymphocytosis
- Adenovirus or RSV co-infection can confuse clinical picture

Complications in infants

- Pneumonia
- Seizures
- Respiratory distress
- Pneumonia
- Encephalopathy
- Death
Pneumonia in Young Infant with Pertussis

- Top chest radiograph taken at admission shows central peribronchial thickening only (arrows)
- Bottom chest radiograph shows widespread consolidation (confirmed by ultrasound) less than 24 hours later

Source of Pertussis in Infants

- Adults transmit pertussis to infants:
  - Among 264 known source-cases:
    - Almost 50% were parents, most often mothers
    - 51% were adults >19 years of age

Pertussis Diagnostics

- Culture: considered gold standard and very specific but insensitive, not timely
- PCR: increased sensitivity > culture, more rapid
- (Ct cut off values are important; contamination of NP swabs with pertussis vaccine DNA can lead to false positives* )
- Serology: useful for adolescents & adults in the later stages of the disease

*See: http://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnostic-pcr-bestpractices.html

Treatment/Prophylaxis

- Treatment (azithromycin/erythromycin) effective for limiting infectivity, but useful for ameliorating symptoms only if started very early in course of disease (catarrhal stage)

- Prophylaxis
  - Identifying contacts difficult
  - Long infectious period
  - Large Ro
  - One strategy is to target prophylaxis to those at highest risk of severe disease (infants <1 year of age) or those in contact with infants
Vaccine

- In US-whole cell vaccine no longer available, acellular (subunit vaccine, purified inactivated components)
- DTaP
  - Pediatric, approved for 6 week-7 years
  - (2,4,6 months, 15-18 months, 4-6 years)
- Tdap
  - >10 -64 years (Boostrix)
  - 11-64 years (Adacel)

Why has there been a U.S. pertussis resurgence since the 1990s?

- Acellular vaccines, which were recommended in the U.S. in 1992 for the 4th/5th doses and for all five doses in 1997 are less reactogenic, but less effective than whole cell vaccines
- General availability of more sensitive laboratory tests (PCR)
- More rapid waning of vaccine-induced immunity from acellular vaccines?
- Genetic changes in B. pertussis?

Case 5

3 year old female with fever and runny nose followed by a rash 3 days later. On exam child is irritable and coughs frequently. Eyes are red and erythematous MP rash whole body, most pronounced on trunk. No palmar erythema, no puffy hands/feet

Labs
- CRP =2, ESR=36
- CBC unremarkable
- AST slight increase, ALT nl
- U/A with pyuria
Case 5

Past Medical history:
- 6 older siblings, incomplete vaccination
- no prior medical problems
- No animal contact
- Just returned home from Philippines

What is the most likely diagnosis
1. A. Kawasaki
2. B. Leptospirosis
3. C. Cat Scratch Disease
4. D. Roseola
5. E. Measles

Measles
Background

- Rash illness, historically childhood infection with 2-4 year epidemic cycle; most cases in winter / spring
- Complications may include otitis media, pneumonia, encephalitis, miscarriage, and death
- Airborne spread - probably the most infectious communicable disease; \( R_0 = 15-17 \)
- Two doses of MMR vaccine offer \( >99\% \) protection from disease; however, requires very high population immunity to interrupt transmission (92-95%)
### Clinical Features

- **Prodrome** – onset 8 to 12 days after exposure (range=7-21 days)
  - Stepwise increase in fever to 101º F or higher
  - Cough, coryza, conjunctivitis
  - Koplik spots (rash on mucous membranes)

### Measles Clinical Features

- **Rash**
  - 2-4 days after prodrome, 14 days after exposure
  - Maculopapular, becomes confluent
  - Begins on face and head
  - Persists 5-6 days
  - Fades in order of appearance

### Measles complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0.1</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>18</td>
</tr>
<tr>
<td>Death</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Based on 1986-1992 Surveillance data*