Emergent Cases in Pediatric Infectious Diseases

Pediatric Emergency Preparedness Seminar Training
May 19, 2015 9:00 – 10:00 AM
University at Albany School of Public Health

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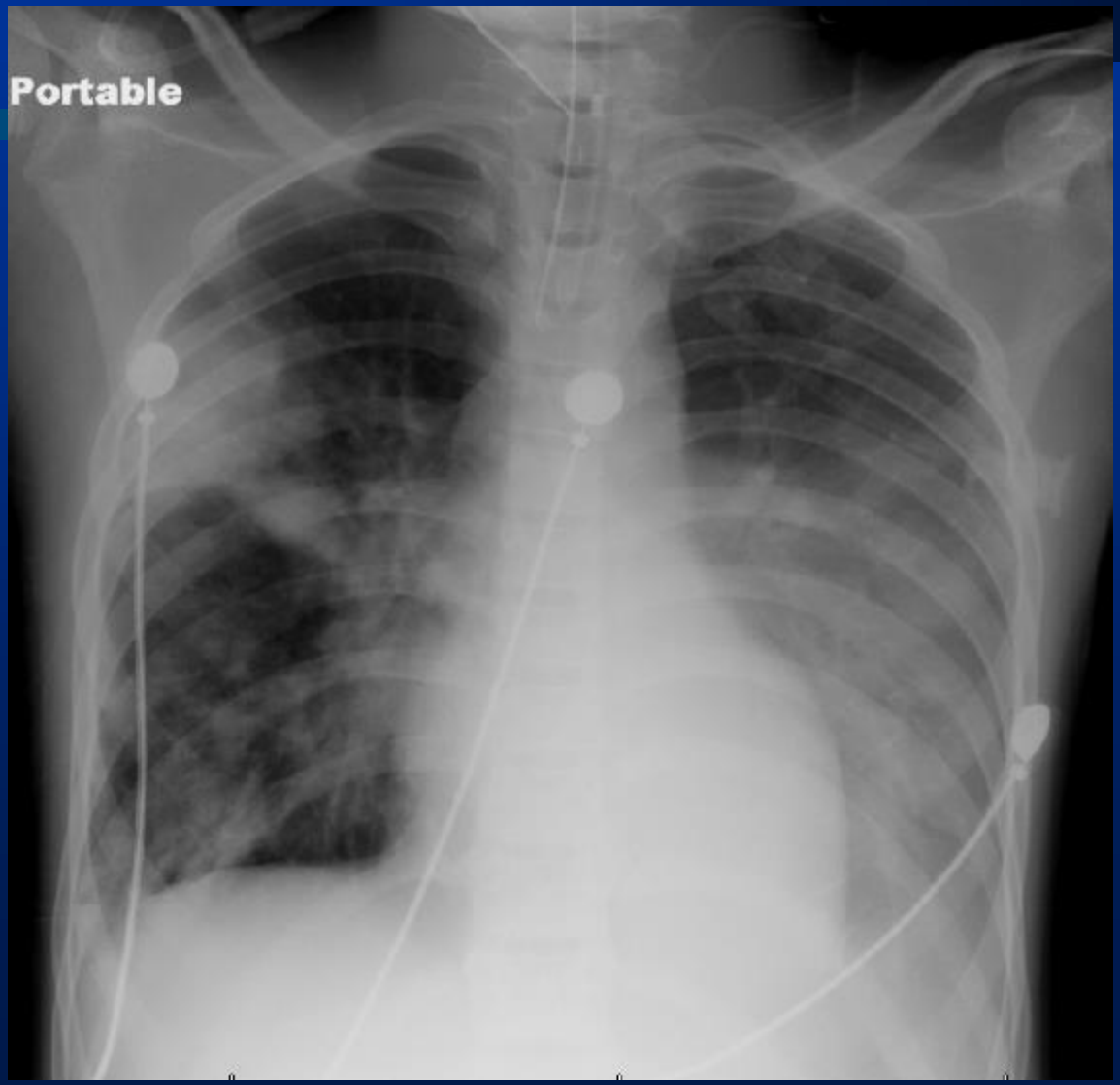
DISCLOSURE

Site Principal Investigator, Duke Clinical Research Institute & Cempra Pharmaceuticals – Research Funding to Albany Medical College

GOALS

- Identify clinically emergent infectious diseases through visual diagnosis.
- Describe the clinical course of emergent infectious diseases.
- Review evidenced-based recommendations in the management of emergent infectious diseases.

Fever & Neutropenia



Fever & Neutropenia

- 10 yo previously healthy, cough, fever 103 ^{o}F
  - Chest pain (left > right), shallow breathing & poor respiratory effort, O_2sat 88%, incoherent prompting intubation
- CBC – WBC 0.7, Hgb 10.3, platelet 144,000
  - ANC 200, ALC 400; rapid flu test negative
- PICU, Peds ID
  - 10 yo, fever neutropenia, bilateral pneumonia

Fever & Neutropenia (International Guideline for Peds)

- Fever & neutropenia
  - Use of monotherapy with antipseudomonal β-lactam as empiric tx for fever & neutropenia
  - Cefepime was empirically started
  - Add glycopeptide for patients who are unstable, when resistant infection is suspected (e.g. history of MRSA), or for centers with high rate of resistant pathogen (AMC antibiogram, MRSA)
  - Vancomycin & clindamycin (inhibit toxin production)

Lehrnbecher T, et al. J Clin Oncol 2012;30:4427-38

Fever & Neutropenia

- Neutropenia
  - Transient mild to moderate neutropenia can be caused by common viral infections such as RSV, influenza A & B, and parvovirus.
  - In most cases, neutropenia occurs during the first few days of the viral illness & persists for 3 to 8 days
  - Request for NP swab for respiratory viral PCR panel & start empiric oseltamivir (peramivir)
  - Additional history: was not flu vaccinated

Segel GB & Halterman JS. Pediatr Rev 2008;29(1):12-23

UPDATE – Flu Vaccine

- 2014-15 Influenza Vaccine (unchanged from the 2013-14)
  - Trivalent: H1N1 (A/California/7/2009)
    H3N2 (A/Texas/50/2012- like)
    B/Massachusetts/2/2012 - like
  - Quadrivalent: Trivalent strains
    B/Brisbane/60/2008 - like
  - Based on global influenza virus surveillance

Pediatrics. 2014 Sep 22. pii: peds.2014-2413. [Epub ahead of print]

Unprotected Flu Strain

- 91% of flu (+) tests (1,200 specimen) were due to flu A and 9% flu B
  - Nearly all flu A were H3N2 (Switzerland strain)
  - ~50% were antigenically different from the H3N2 vaccine component
  - Antigenic drift (vH3N2), accumulation of point mutations causing minor changes in the genes encoding for HA & NA proteins

Flannery B. MMWR. 2015;64:10-15; http://www.healio.com/infectious-disease
Dawood FS, et al. Chapter 229 Influenza Virus – Principles and Practice of Infectious Disease, 4th edition; p. 1149

- Flu vaccine effectiveness is low (23%)

Flannery B. MMWR. 2015;64:10-15

http://www.cartoonstock.com/directory/i/inoculation.asp

Rapid Diagnostic Flu Test

- 10 FDA approved for screening flu
  - Results in 15 min
  - Sensitivity 50-70%, specificity 90-95%
  - Accuracy depends on prevalence, i.e. false negative likely to occur with high prevalence
  - A negative rapid flu test does not r/o flu

http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

AMC Microbiology as of Feb 2013

- The following organism types & subtypes are identified using the FilmArray RP:
  - Adenovirus, Coronaviruses HKU1, NL63, OC43, & 229E, hMPV, Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype 2009 H1, Influenza B, Parainfluenza Viruses 1, 2, 3, & 4, Rhinovirus/Enterovirus, and RSV
  - Turn around time ~2 hours

Adjuctive Therapies

- Clindamycin
  - Some experts consider this agent in necrotizing/ cavitary pneumonia or severe sepsis
  - Inhibit production of STSS toxin 1 & PVL
- IVIG
  - Less clear in the management of invasive MRSA disease
  - Neutralizes staphylococcal exotoxins e.g. PVL

Liu C, et al. Clin Infect Dis 2011;52:1-38

IV Peramivir

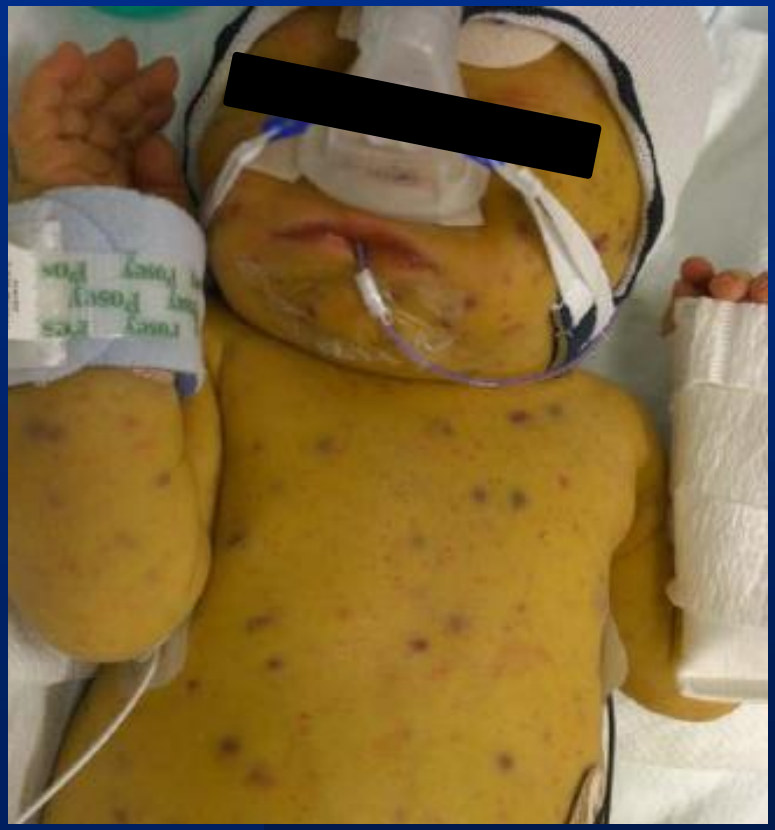
- Emergency use authorization 2009-10 H1N1
- FDA approved - 1st neuraminidase inhibitor for IV administration
- Similar efficacy to PO oseltamivir
- Off label use in hospitalized patients with severe influenza
- Indication: Severe bilateral pneumonia, ANC 200, with concerns for malabsorption

The Medical Letter 2015;57(1461): 17-19 Available at http://secure.medicalletter.org/TML-article-1461b

Fever & Neutropenia

- 10 yo previously healthy, bilateral severe pneumonia, febrile & neutropenia associated with flu B & MRSA
  - Cefepime & vancomycin
  - Clindamycin & IVIG
  - Oseltamivir & peramivir
  - Transferred to a hospital in Boston for ECMO regarding ARDS

Blueberry Muffin Rash



- Congenital rubella
- Meningococcemia
- Congenital CMV
- Intrauterine infections & hematologic disorders

Dobson SR. UpToDate 2014 – Congenital Rubella Syndrome
Bar-Oz B, Loughran B. Emerg Infec Dis 2003;9(6): 7578

Blueberry Muffin Rash

- Initially described with congenital rubella due to extramedullary dermal erythropoiesis
  - In the setting of profound anemia
- Pathophysiology is not clear
  - Hematopoietic stem cells migrate from the bone marrow & settle in the skin
  - Or dermal mesenchymal cells differentiate in situ into blood-producing cells

http://neoreviews.aappublications.org/site/case49/experts.xhtml

Blueberry Muffin Rash

- Newborn term baby transferred from OSH
  - Generalized blueberry muffin rash, jaundice, increase work of breathing, subcostal retractions on CPAP, hepatosplenomegaly
- CBC – WBC 13, Hgb 14, platelet 9,000
  - Mother rubella immune, HIV (-), RPR (-)
- NICU, Peds ID
  - 1 day old Blueberry muffin syndrome, congenital CMV, CMV PCR (+) in blood & urine

Blueberry Muffin Rash

- Ganciclovir 6 mg/kg IV q12h, 21 days
- Valganciclovir 16 mg/kg PO q12 hr, up to 6 mos.
  - Treatment recommended for symptomatic congenital CMV disease, with or without CNS involvement
  - Treatment should start in the 1st month of life
  - Benefit for hearing loss and neurodevelopmental outcomes

Bradley JS (Eds). Nelson's Pediatric Antimicrobial Therapy 2015; 21st ed.:21

Blueberry Muffin Rash

- Most common side effects: neutropenia
  - 68% in IV ganciclovir
  - 20% in PO valganciclovir
- Some patients responds to G-CSF or discontinuation of therapy

Bradley JS (Eds). Nelson's Pediatric Antimicrobial Therapy 2015; 21st ed.:21

6 months versus 6 weeks

- IV GCV x 6 weeks improves audiologic outcomes at 6 months but the benefits wane over time
- RCT PO VGC with symptomatic congenital CMV comparing 6 months vs. 6 weeks of tx
  - 1º end point change in hearing in the best ear from baseline to 6 months
  - 2º end point change in hearing in the best ear from baseline to 12 – 24 months, neuro-development

Kimberlin D, et al. N Engl J Med 2015; 372:933-43

6 months versus 6 weeks

- N = 96, of whom 86 with follow-up data at 6 months
  - Hearing outcome at 6 months is similar (P=0.41)
  - Hearing outcome at 12 months is significantly better in the 6 month tx arm vs. the 6 week tx arm (73% vs. 57%, P=0.01)
  - Hearing outcome at 24 months is significantly better in the 6 month tx arm vs. the 6 week tx arm (77% vs. 64%, P=0.04)

Kimberlin D, et al. N Engl J Med 2015; 372:933-43

6 months versus 6 weeks

- Neurodevelopmental scores at 24 months is significantly better in the 6 month tx arm vs. the 6 week tx arm
  - 3rd ed, Bayley Scales of Infant & Toddler Dev.
  - Language composites (P=0.004)
  - Receptive-communication scale (P=0.003)
- Grade 3 or 4 neutropenia
  - No difference in the 6 month tx arm vs. 6 week tx arm (21% vs. 27%, P=0.64)

Kimberlin D, et al. N Engl J Med 2015; 372:933-43

6 months versus 6 weeks

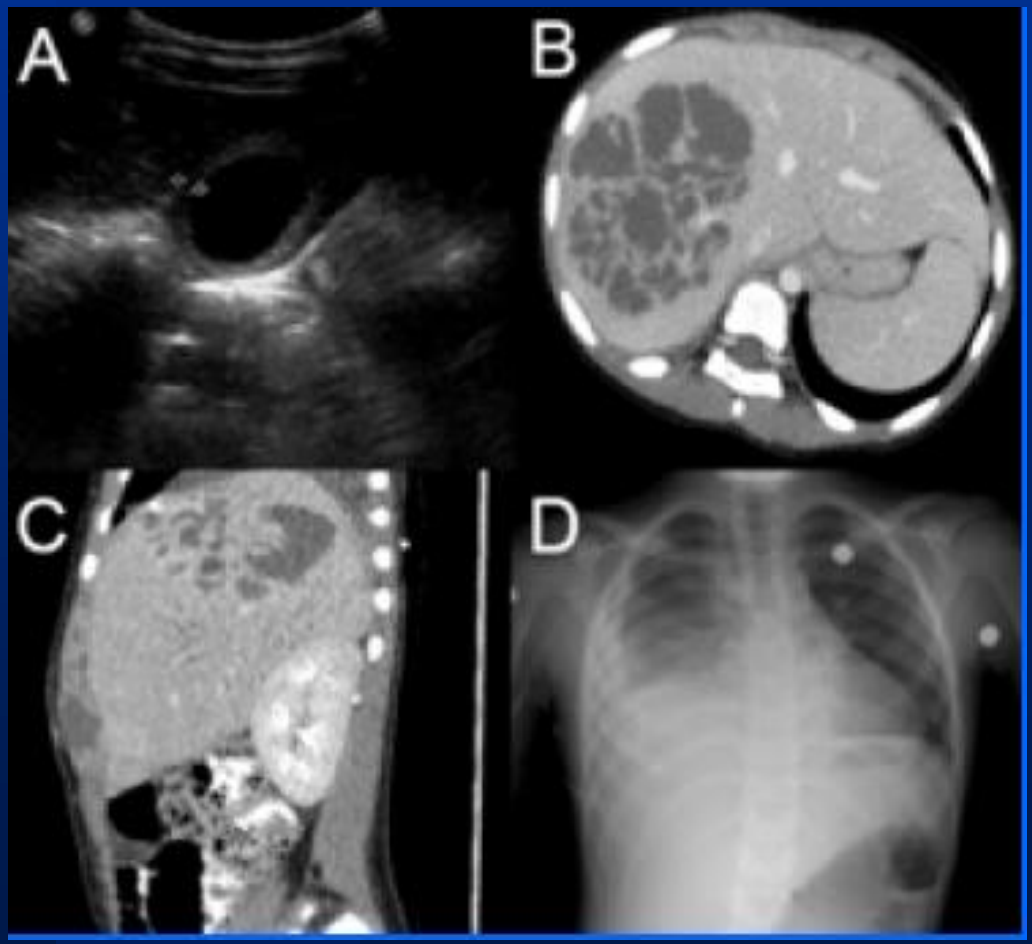
- Treating symptomatic congenital CMV disease with valganciclovir for 6 months as compared to 6 weeks did not improve hearing in the short term but appeared to improve hearing and developmental outcomes modestly in the longer term.

Kimberlin D, et al. N Engl J Med 2015; 372:933-43

Blueberry Muffin Rash

- 2 month old infant with symptomatic congenital CMV, bilateral hearing loss
  - IV ganciclovir then PO valganciclovir
  - Neutropenia (ANC <500) improved after VGC dose adjustment
  - Needs close follow up for audiology & neurodevelopmental monitoring

Primary Liver Abscess



- A. US of the abdomen
- B. CT scan of abdomen (liver)
- C. CT scan of abdominal wall
- D. CXR

Kumar JA, Santos RP, et al. AAP-National Conference Exhibit 2010

Primary Liver Abscess

- 7 yo previously healthy female with nausea, diarrhea, severe abdominal pain, fever, & hypotension hospitalized with concern for sepsis.
  - No history of travel to endemic areas in Asia
- US of the abdomen showed a multiloculated mass in the right hepatic lobe.
  - A CT guided drainage obtained 200-mL of purulent material which yielded glistening mucoid colonies.

Kumar JA, Santos RP, et al. AAP-National Conference Exhibit 2010

Primary Liver Abscess

- *K. pneumoniae* was isolated & was string test positive consistent with the hypermucoviscosity phenotype.
- A string of mucus ≥5 mm from a mucoid colony is considered positive. (Fang C. et al 2004)

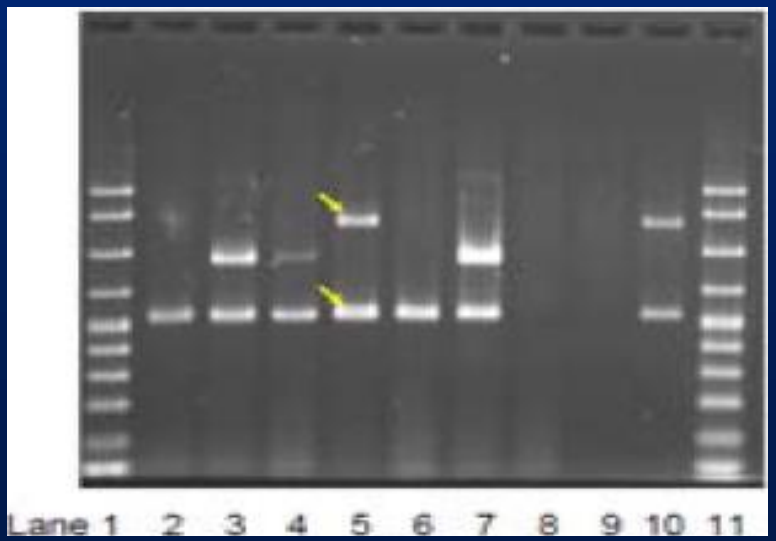
Kumar JA, Santos RP, et al. AAP-National Conference Exhibit 2010

Primary Liver Abscess

- Her hospital course was complicated with bacteremia, cholecystitis status post open cholecystectomy, & right pleural effusion requiring drainage & chest tube placement.
  - Improved while on antimicrobial regimen (≥3 weeks)

Primary Liver Abscess

- PCR for detection of virulence factors – magA, rmpA, wyzK2 genes. Lane 5 shows the patient's *K. pneumoniae* isolate positive for magA (top band) and rmpA (lower band).



Kumar JA, Santos RP, et al. AAP-National Conference Exhibit 2010

Primary Liver Abscess

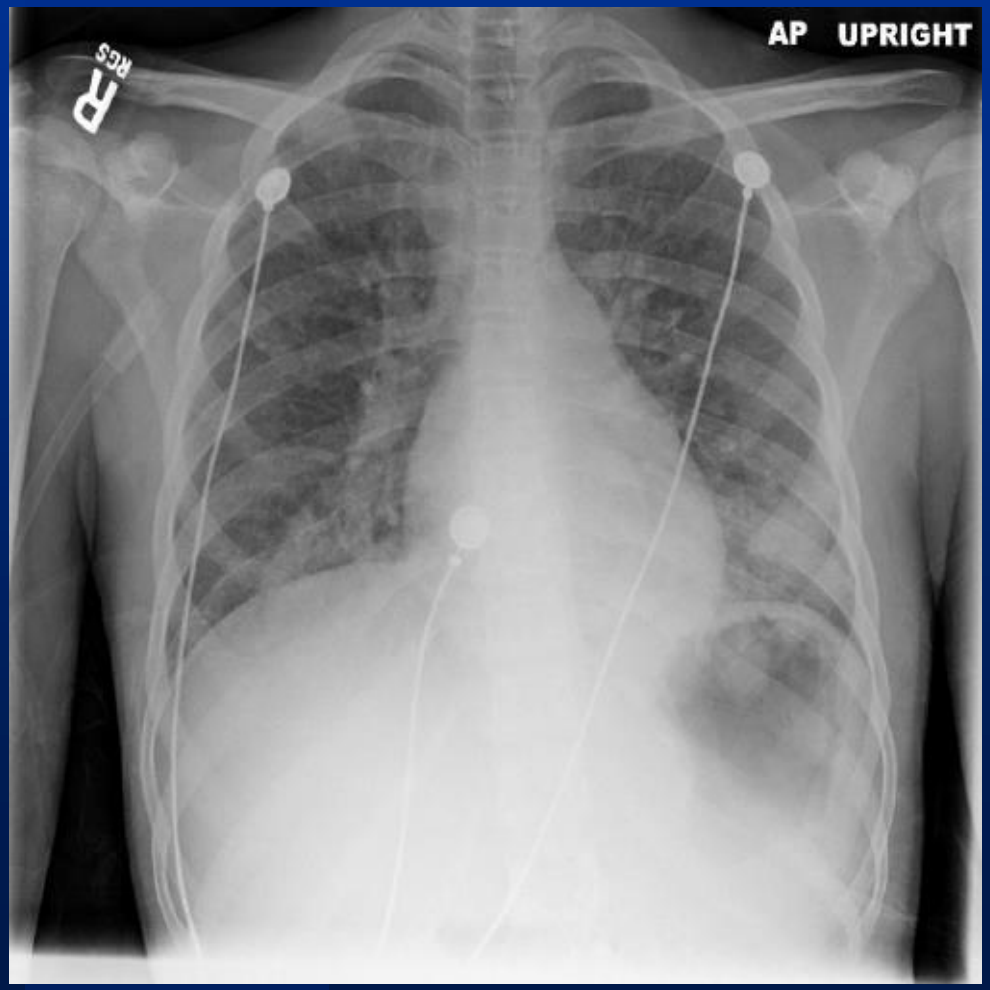
- Molecular studies showed the presence of both magA associated with virulence through K1 serotype expression & rmpA, a regulator of capsular polysaccharide synthesis.
  - Consistent with hypermucoviscosity phenotype.
  - Hypermucoviscosity phenotype (e.g. glistening mucoid colonies, string test positive) should prompt clinicians to look for other foci of infections.

Kumar JA, Santos RP, et al. AAP-National Conference Exhibit 2010

Primary Liver Abscess

- This is an emerging disease due to the absence of traditional risk factors such as chronic medical conditions & exposure to endemic areas.
- This is the first case report of *K. pneumoniae* isolate with genotypic characteristics similar to those reported in Asia (magA+ & rmpA+) causing invasive disease in a previously healthy child.

HIV (+) with Dyspnea

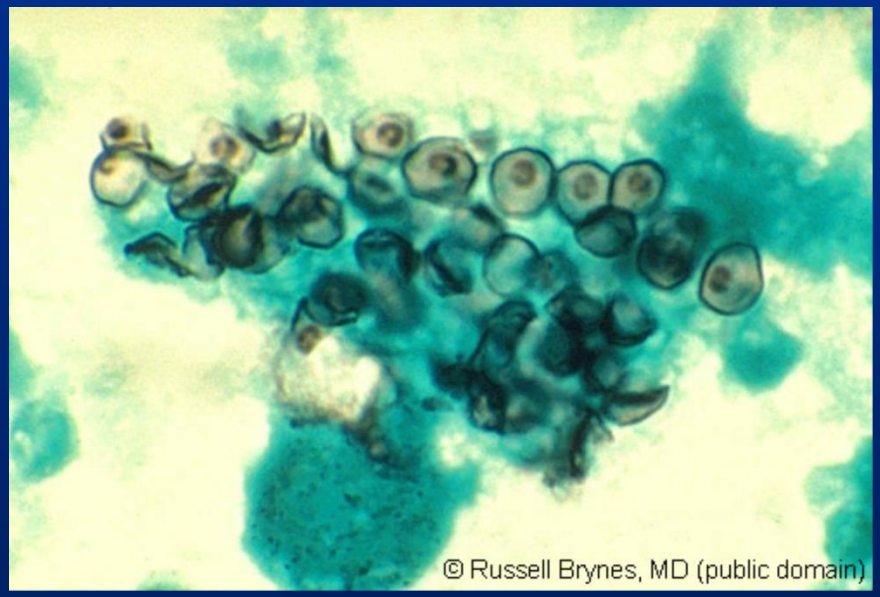


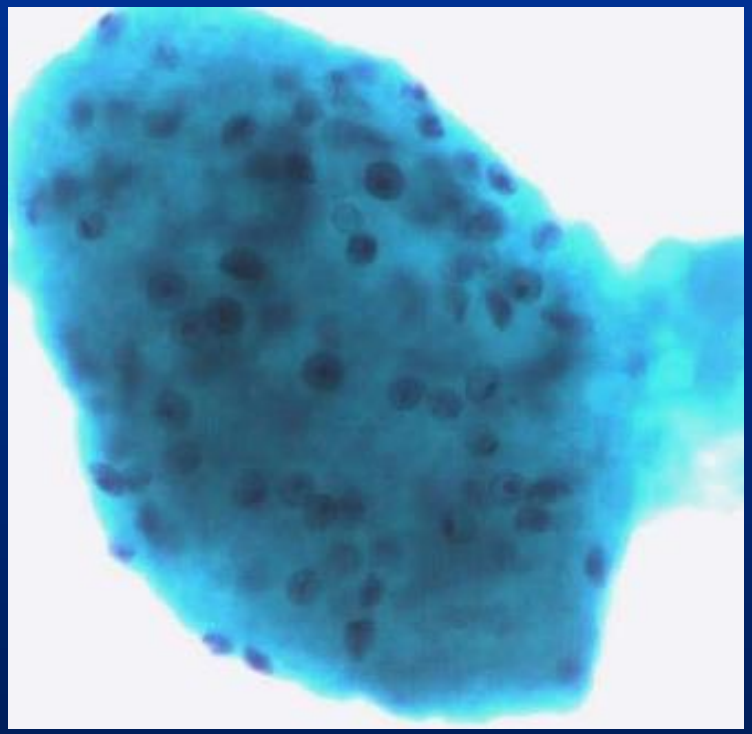
- Right lower lung consolidation, likely representing pneumonia.

HIV (+) with Dyspnea

- 17 yo perinatally infected with HIV (AIDS) admitted for respiratory distress presenting with fever, cough, increase work of breathing
  - Temp 37.9 ^{o}C, BP 76/39, HR 146/min, RR 20/min, no hypoxemia (O_2 sat 96%, in room air)
  - HIV VL 230,000 copies/mL, CD_4 6 cells/cmm
  - Bacterial pneumonia
  - Complicated with Candida esophagitis & diarrhea

HIV (+) with Dyspnea





- Cysts of *P jirovecii* in a smear from BAL (GMS stain).

Brynes R. Red Book 2012 (online version – public domain)

PCP

- Most children with PneumoCystis pneumonia (PCP) are hypoxic with low arterial O_2.
- Characteristic syndrome of subacute diffuse pneumonitis with dyspnea, tachypnea, O_2 desaturation, nonproductive cough, & fever.
- Mortality rate in immunocompromised patients ranges from 5%-40% with tx & approaches 100% without tx.

AAP. 2015 Red Book – *Pneumocystis jirovecii*; 30th ed:638-44

PCP

- CXR often show bilateral diffuse interstitial or alveolar disease; rarely, lobar, cavitary, miliary, & nodular lesions or even no lesions are seen.
- A definitive diagnosis of PCP is made by visualization of organisms in lung tissue or respiratory tract secretion specimens.

AAP. 2015 Red Book – *Pneumocystis jirovecii*; 30th ed:638-44

PCP

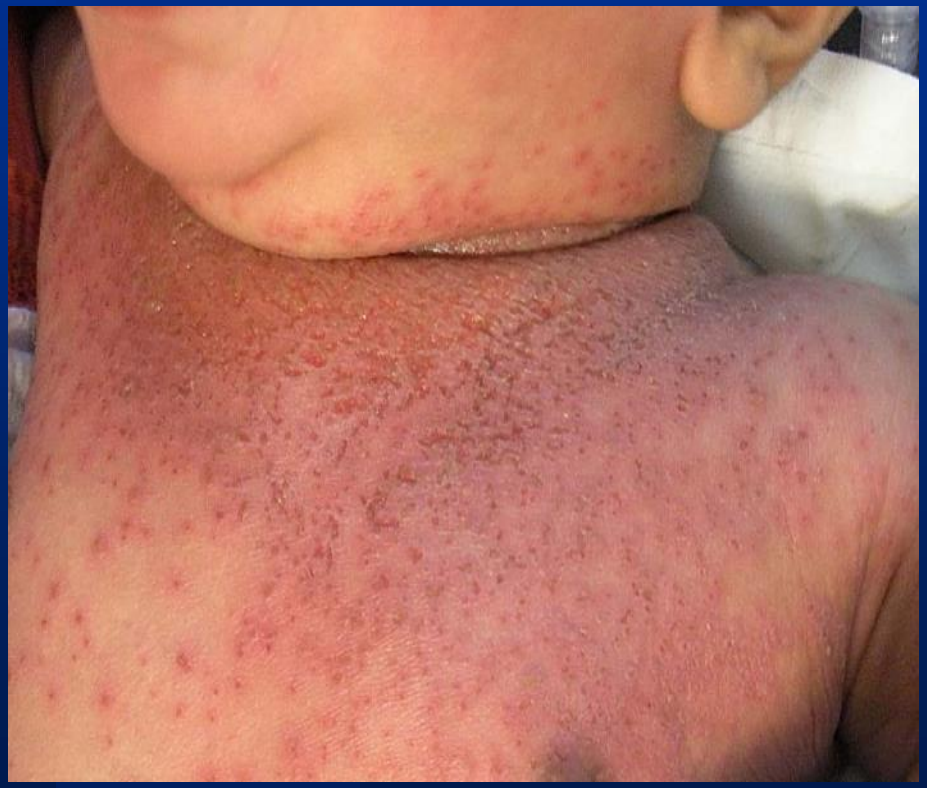
- PO TMP-SMX for with mild disease or with good response after initial IV tx or those without malabsorption or diarrhea
  - Duration of therapy is 14-21 days.
- In patients with AIDS, secondary prophylaxis should be initiated after tx for acute infection.

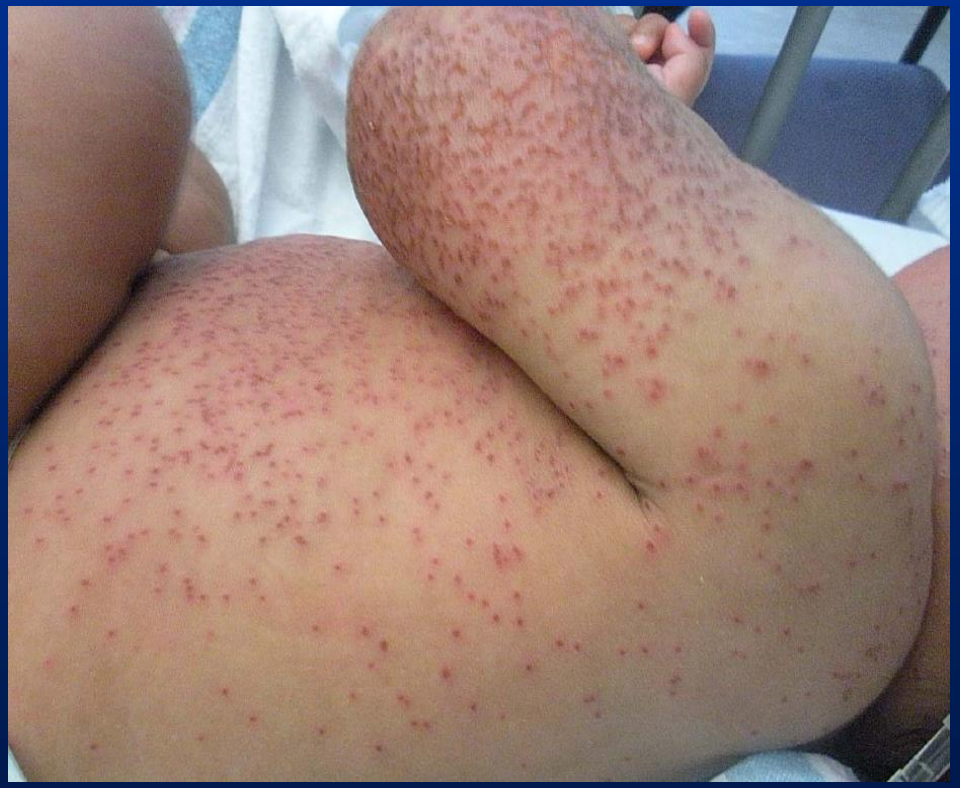
AAP. 2015 Red Book – *Pneumocystis jirovecii*; 30th ed:638-44

HIV (+) with Dyspnea

- 17 yo perinatally infected with HIV with AIDS
  - TMP-SMX for 3 weeks for PCP then 2nd prophylaxis with TMP-SMX SS
  - Fluconazole for candida esophagitis for 3 weeks then suppressive regimen
  - MAC prophylaxis was offered
  - cART – RPV/TDF-FTC QD + RAL BID

Generalized Rash & Fever





Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA

Generalized Rash & Fever

	CLINICAL PRESENTATION
Demographics	N = 3, 4 mos. – 7 years old
Chief Complaint	Severe eczema flare up
Period	Mar – Aug, 2011
Symptoms	Oral ulcers not common
	History of fever
	Vesicular rash with exacerbation
Signs on Presentation	All were febrile, toxic looking
Past Medical History	All with atopic dermatitis
Family History	(+/-) Sick contact
Treatment	IV acyclovir, 2ndary bacterial

Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA

Generalized Rash & Fever

- 3 male children with eczema exacerbation associated with HSV1 (eczema herpeticum)
  - Patient A, 4 mo
  - Patient B, 7 yo
  - Patient C, 10 mo
- Worsening of the disease while on acyclovir
  - Patient A, with MSSA bacteremia
  - Patients B & C, with diffuse facial cellulitis involving both eyelids due to MSSA

Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA

Generalized Rash & Fever

- All patients improved after completing acyclovir regimen & ~10 days of antibiotics
  - Patient A, cefazolin
  - Patient B, clindamycin
  - Patient C, cefazolin
- No recurrence of EH while on suppressive acyclovir regimen (10 mg/kg PO BID) & vitamin D supplements

Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA

Eczema Herpeticum (HSV1)

- Eczema herpeticum (EH) is a dermatologic emergency associated with herpes simplex virus (HSV) type 1 viremia.
- HSV viremia had been rarely described in immunocompetent and more commonly among immunocompromised children.

Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA
Stollery N. The Practitioner 2011;255(1738):32-3
Diamond C, et al. Pediatr Infect Dis J 1999;18(6):487-9
Stanberry LR, et al. Clin Infect Dis 1994;18:401-7

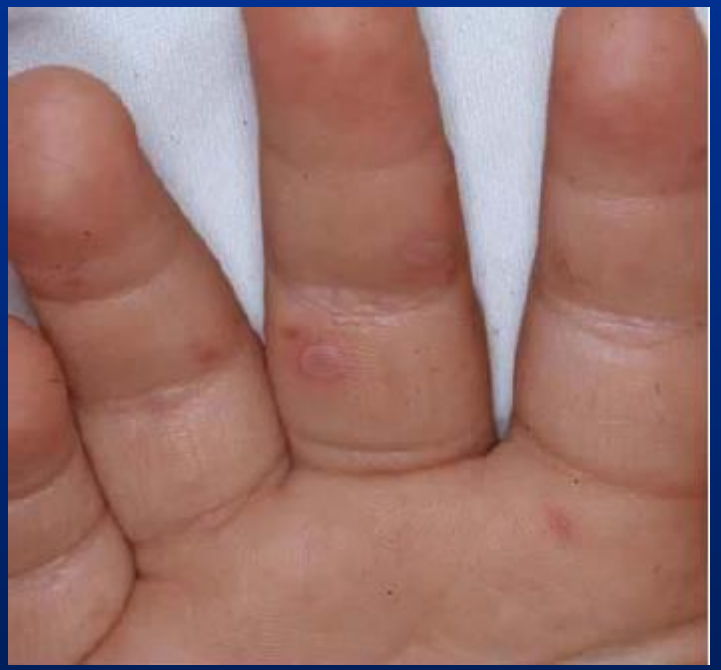
Eczema Herpeticum (HSV1)

- Improved clinical outcome requires prompt recognition of EH since delayed (>1 day) acyclovir initiation is associated with prolonged length of hospital stay.
  - In our patients, systemic antiviral agents were given within 24-48 hours of clinical presentation.

Santos RP, et al. ID Week 2012 (Poster Presentation); San Diego, CA
Aronson PL, et al. Pediatrics 2011;128:1161-7

Another Rash & Fever

- Hand-foot-mouth disease, Coxsackievirus A16

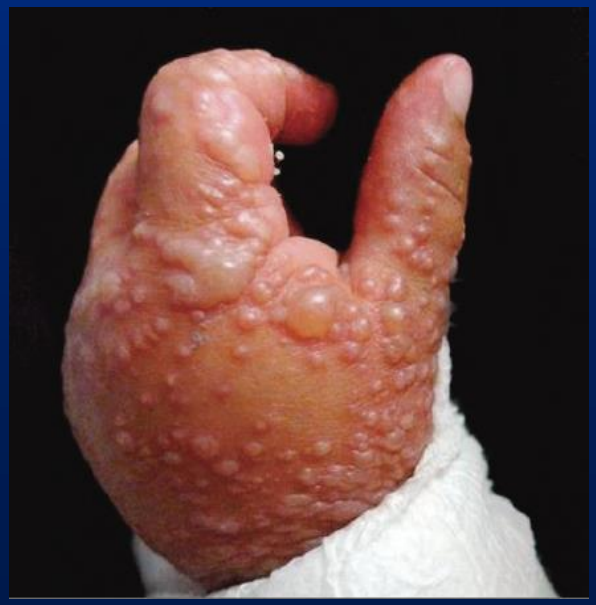


http://www.mayoclinic.org/diseases-conditions/hand-foot-and-mouth-disease/basics/symptoms/con-20032747

McIntyre MG, et al. MMWR 2012;61:213-4

INTRODUCTION

- Atypical cases of EV infection in children were described in Alabama, California, Connecticut, and Nevada from Nov. 2011 – Feb. 2012



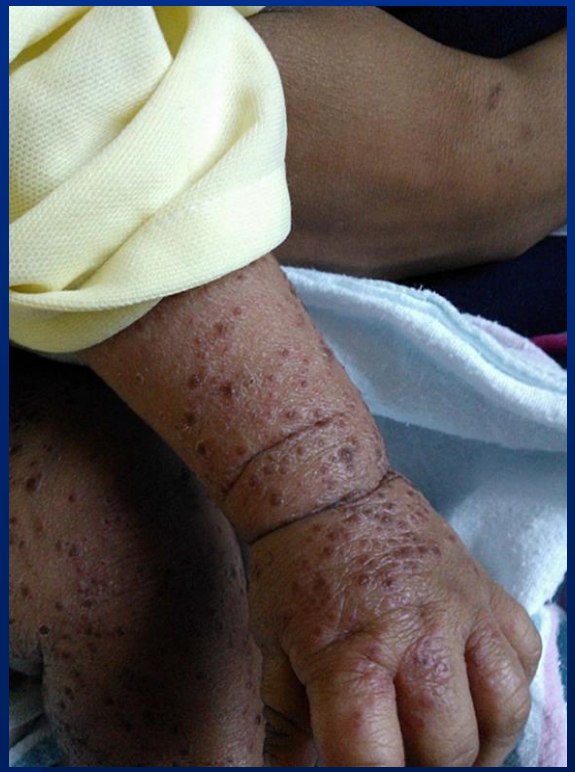
McIntyre MG, et al. MMWR 2012;61:213-4, Meissner HC. AAP News 2012;33;1

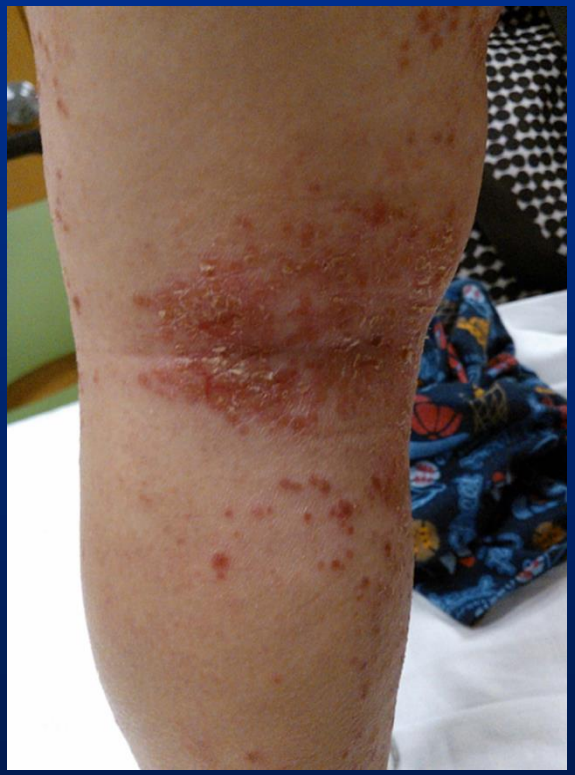
CLINICAL PRESENTATION

	CLINICAL PRESENTATION
Demographics	N = 4, 4 mos. – 9 years old
Chief Complaint	Severe eczema flare up
Period	May – Oct, 2012
Symptoms	All with ulcers in posterior pharynx
	History of fever (1-5 days)
	Vesicular rash with exacerbation
Signs on Presentation	All were afebrile, not toxic looking
Past Medical History	All with atopic dermatitis
Family History	All with sick contact
Treatment is supportive	Except in the 4 mos. old infant

Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013

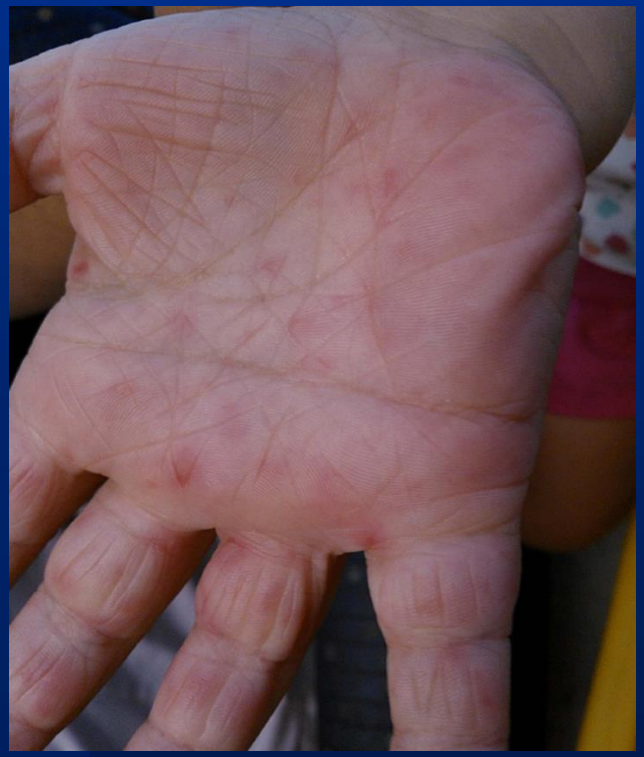
- Hand & arm of a 4 month old
- Lower extremity of a 1.5 year old

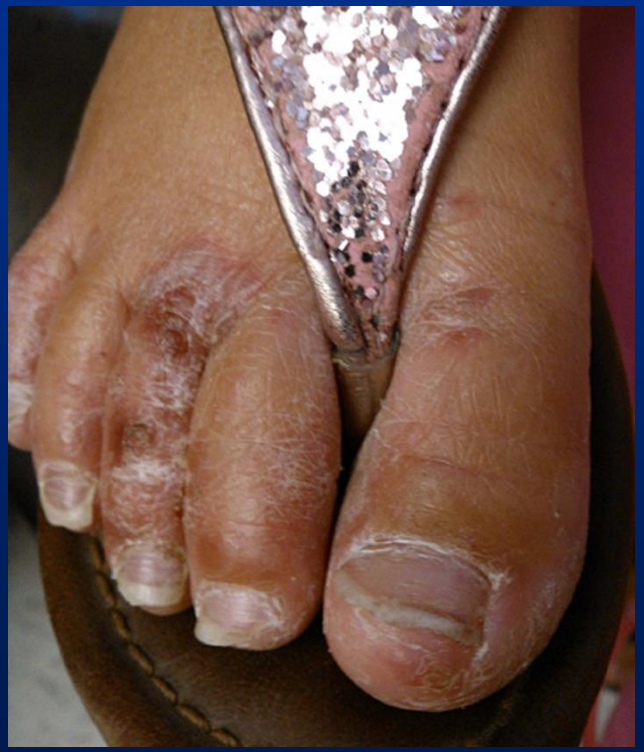




Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013

- Hand & foot of a 9 year old





Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013

Kaposi Varicelliform Eruption

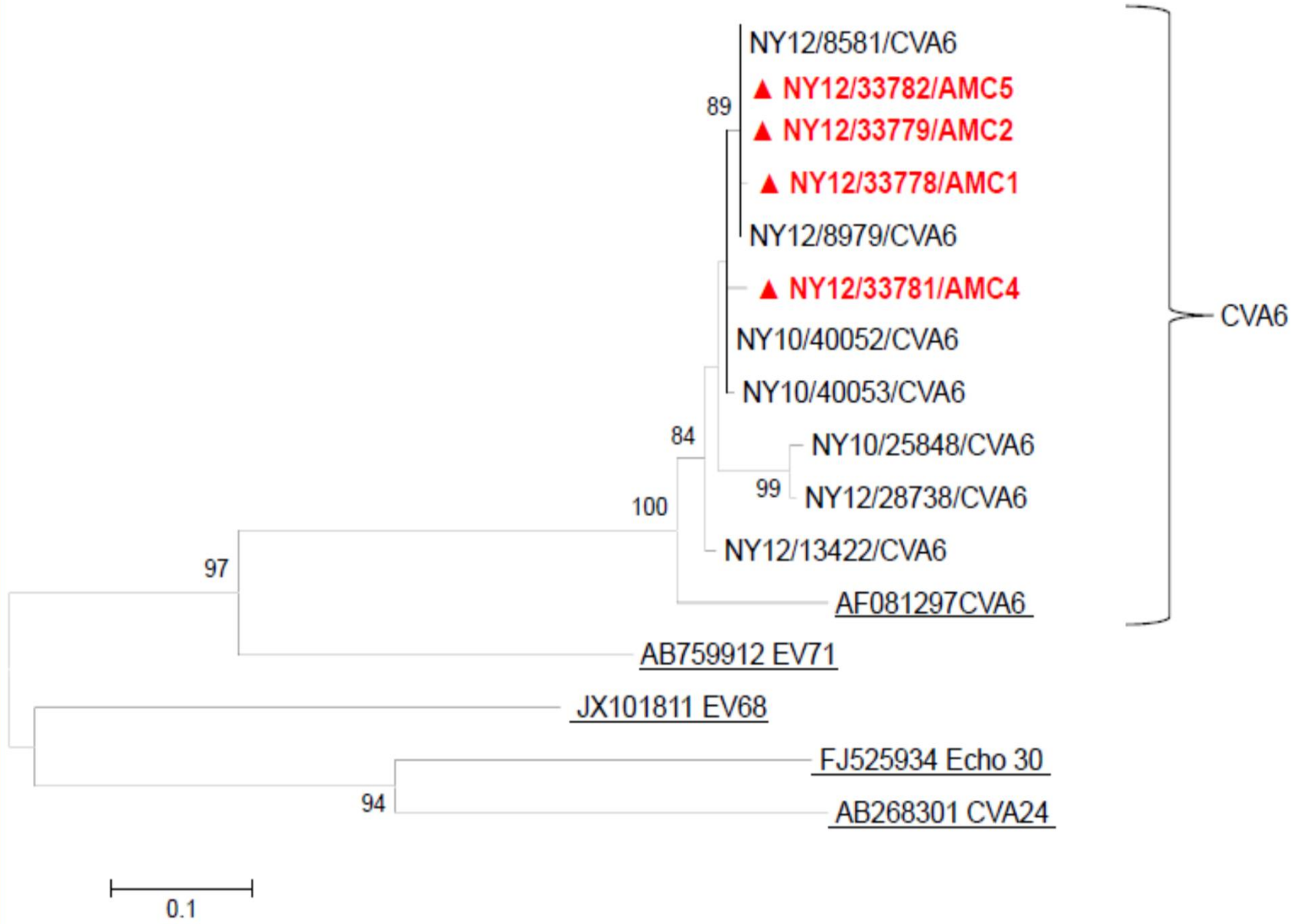
- Disseminated EV infection in the setting of underlying skin disease such as eczema or atopic dermatitis is consistent with Kaposi varicelliform eruption (KVE).

Kramer SC, et al. Cutis 2004;73:115-22
Lavigne KA & Hossler EW. Medscape – KVE Oct 2014

LABORATORY TESTS

	RESULTS
EV PCR from oral/throat swabs	(+) in A, B (Qualitative)
	A, 4.12 log copies/mL B, 5.16 log copies/mL
EV viremia	(+) in A, C (Qualitative)
	A, 2.15 log copies/mL C, 3.75 log copies/mL
Partial sequencing of VP1	Coxsackievirus A6 (CVA6)
Phylogenetic Analysis	All CVA6 isolates in one cluster (99% identity)

Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013



Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013

Kaposi Varicelliform Eruption

- Enterovirus infection can have protean manifestations (rare presentation of a common disease)
- Kaposi varicelliform eruptions (KVE) due to coxsackievirus A6 is benign & requires supportive care
- The atypical presentation of CVA6 infection may be further modified in KVE which may be confused with HSV or VZV infections.

Santos RP, et al. Pediatric Academic Societies, Abstract #754302. Washington, D.C. May 2013
Flett K, et al. Emerg Infect Dis 2012;18(10):1702-3

TAKE HOME MESSAGE

- Identified clinically emergent infectious diseases through visual diagnosis.
- Described the clinical course of emergent infectious diseases.
- Reviewed evidenced-based recommendations in the management of emergent infectious diseases.
- When in doubt, call Peds ID