Hospital of the University of Pennsylvania

Citywide Infectious Disease Conference
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Presentation

60's year old woman initially presented to an OSH with diarrhea and vomiting x 5 days

- Loose, liquid, nonbloody stools, denies fever
- Vitals: 177/86, HR 69, RR 18, 100% on RA, Temp? "afebrile"
- NAD, nontoxic appearing
- Initial labs significant for:
  - WBC 15.5, (88% PMNs, 8% lymphs, 4% monos)
  - Na 127, Glu 181, Cl 90, Cr 0.7
  - Normal LFTs
  - Enteric pathogen panel neg

At the OSH

Day #2

Continued diarrhea, vomiting, put on liquid diet, not tolerating PO

Confusing words: “she was calling her cat, Teddy, a puppy”

- Hyponatremia 127 to 118 → fluid restriction, salt tablets, 3% saline
- Cr 0.7 → 1.7
- K 2.8
- WBC 15 → 20

Day #3, fever to 102.3

Became progressively lethargic → intubated

- Developed bradycardia to 40s and hypotension.
- TTE: mild MR and AI, sinus rhythm 71

Started on Vancomycin and Meropenem

OSH course

HD # 3, MRI head:

- "Nonspecific left parietal calvarial enhancing lesion, which could reflect a hemangioma, although given the history of prior malignancy calvarial metastasis is difficult to fully exclude. Would consider bone scan as clinically warranted."

CT abd/pelvis:

- No acute abnormalities

OSH course continued

- Day #3, LP: 0 WBC, 0 RBCs, normal protein, normal glucose
  - HSV 1,2 neg
  - CrAG neg
  - Gram stain neg
- Respiratory viral panel neg
- HIV neg
- Blood cultures day 1, 3, 4, 9 → no growth
- C. diff neg

PMH

- Cystosarcoma phyllodes of left breast s/p mastectomy 2009
- Subsequent metastatic disease to the pelvis – 2012

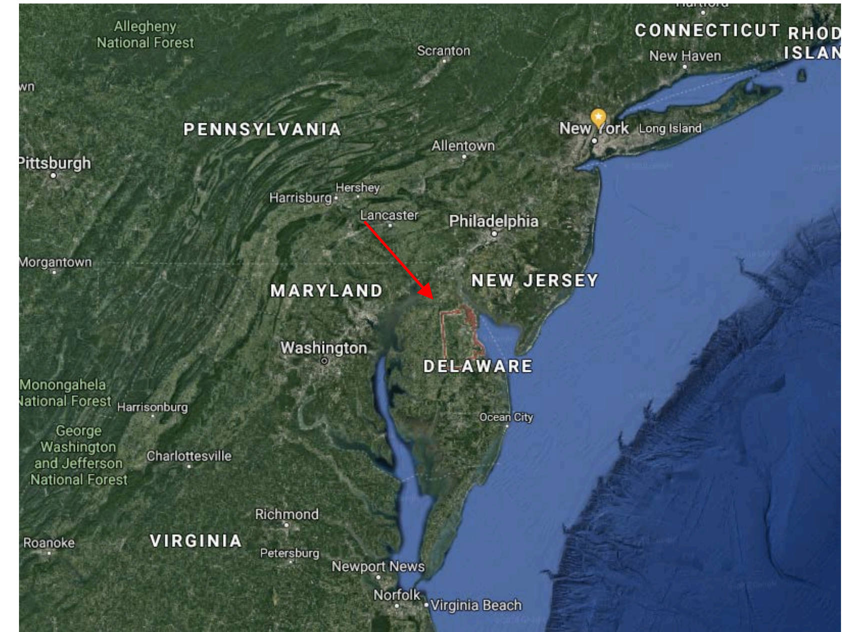
Surgical History:

- Splenectomy
- left nephrectomy
- Hysterectomy
- appendectomy

Social history (obtained from cousin)

- Lives alone
- Not married, no partner, no kids
- Reportedly a “hoarder,” family hadn’t been in house for a while
- 10-12 outdoor cats, maybe one indoor cat
- Works at Dollar Store
- Lives in a rural area of Kent County, Delaware
- No known international travel

- Prior notes indicate no tobacco, drugs, alcohol



At OSH:

- Team orders Bartonella serologies
- Starts Doxycycline and Rifampin on day #8
- Discontinues Vancomycin and Meropenem

Transferred to HUP Neuro ICU day #9

- T 93.3, HR 54, BP 80/52, placed on Bair hugger
- Multiple episodes of asystole between 5-8 seconds, transcutaneous pacemaker placed
- Exam:
  - Intubated, poor dentition, withdraws to painful stimuli
  - +corneal reflex, no gag or cough
  - Bradycardic
- Na 165 on arrival, WBC 20 (88% PMNs)
- EEG showing generalized seizure activity
- Unable to obtain LP initially

Repeat MRI head and LP:

MRI: “FLAIR signal abnormality and gyral swelling in the bilateral medial temporal lobes. No signal abnormality in the deep gray nuclei. Pattern would be most consistent with HSV encephalitis. Additional considerations include limbic encephalitis given history of malignancy, however considered less likely given interval increase in signal abnormality since 7/28/2018”

LP: day #12 (day 3 after HUP transfer)

- WBC 13 (17% PMN, 31% Lymph, 52% monos), 6 RBCs
- Protein 285, Glucose 51

Differential?

Diagnostic studies:

- HIV
- Lyme serologies
- Ehrlichia/Anaplasma
- Quantiferon

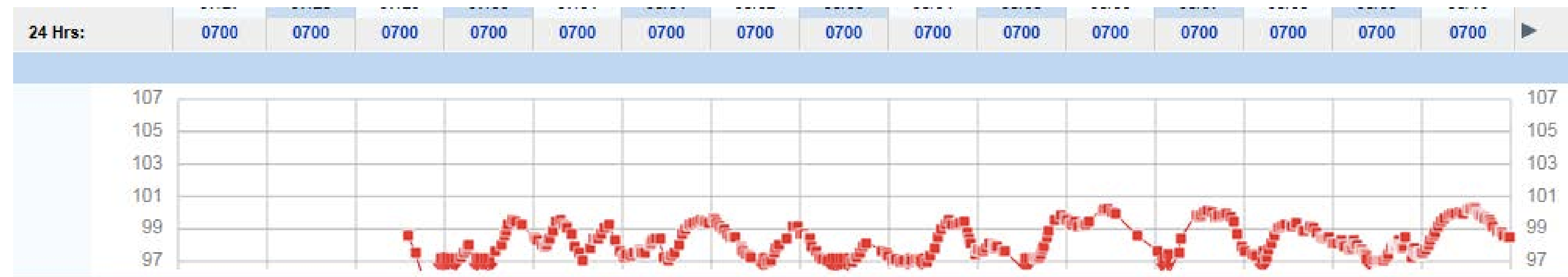
Additional CSF studies

- HSV I, II
- Arbovirus panel (WNV, EEV, WEV, California Encephalitis, St. Louis)
- Bartonella
- Powassan
- Paraneoplastic panel
- NMDAR ab
- RT-QUIC, 14-3-3
- Enterovirus 71
- HHV6

Case, continued

- Initially started on Doxycycline and Ceftriaxone

- Started on high dose steroids, plasma exchange for autoimmune encephalitis
- Primary team adds Ampicillin and Acyclovir



Case, continued

- HUP day #7
  - Attempted brain biopsy, but patient became hypotensive, aborted
  - Started RIPE
  - Sent rabies samples to CDC
  - CSF next-generation metagenomic sequencing sent to UCSF

- HUP day # 12:
  - Called OSH: Bartonella IgG returned positive, titer 1:128
  - Restarted on Doxycycline and Rifampin

Case, continued

- CDC calls back: rejects rabies sample as inadequate, please re-send

HUP day #14

- Rabies studies resent to CDC on HUP day #14
- Although nuchal biopsy accidentally gets dipped in formalin for a few seconds
- Does the five second rule apply?

Case, continued

HUP day #17

- Rabies serum IgG positive, IgM negative
  - RRFIT titer: 1:200
- Rabies CSF IgG and IgM positive
- Saliva PCR negative
- Nuchal biopsy – PCR negative

Final
(Abnormal)

!

Rabies virus neutralizing antibodies were detected by the rapid fluorescent focus inhibition test (RFFIT) at 1:200 (1.6 IU/ml). Complete rabies virus neutralization demonstrated at the 1:5 dilution.
Rabies virus IgG antibodies were detected by the indirect fluorescent antibody test (IFA).
No Rabies Virus IgM Antibodies Were Detected by the indirect fluorescent antibody test (IFA).
Test Performed At Rabies Laboratory, Centers For Disease Control And Prevention (Cdc). Mailstop G33, 1600 Clifton Rd NE, Atlanta, GA 30329.

Case, continued

HUP day #19

- Repeat MRI → worsening T2 signal abnormality
- Repeat serum sent for rabies testing, nuchal biopsy
  - Nuchal biopsy - PCR negative
  - RRFIT titer: 1:210
- Hospital Day #23
  - Family meeting with cousin and family, decides to withdraw care

Postmortem

- Human brain tissue positive for rabies virus antigen by DFA

- Sequencing indicate eastern raccoon rabies virus variant

What about the Milwaukee Protocol?

2004 – 15F from Wisconsin p/w fever, ataxia, obtundation, dysarthria
Bat bite one month prior

- Midazolam + Ketamine, Ribavirin + Amantadine
- Released 76 days later, regained full function, except with residual choreoathetosis and ballismus

- At least 26 subsequent case reports of patients treated with Milwaukee protocol have subsequently died
- Routine use no longer recommended

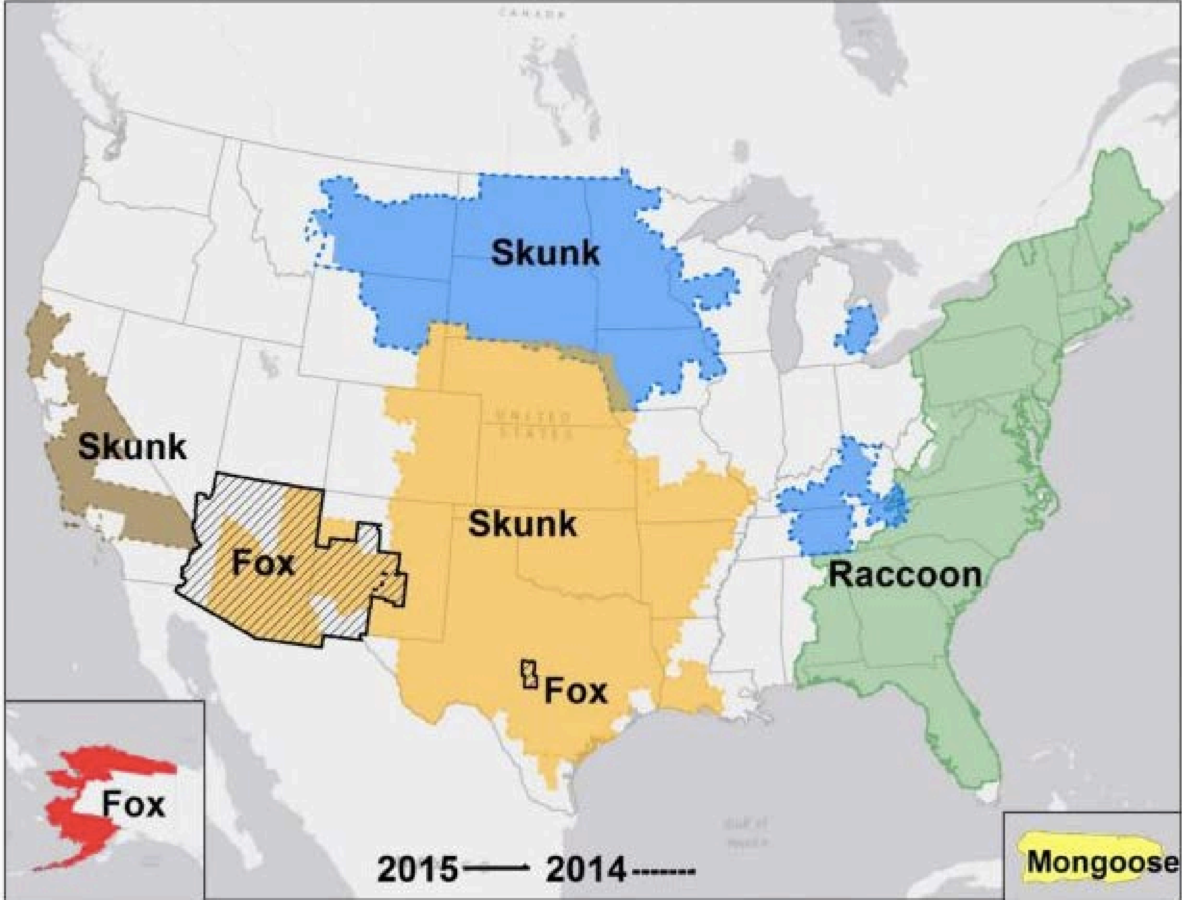
Rabies in the United States

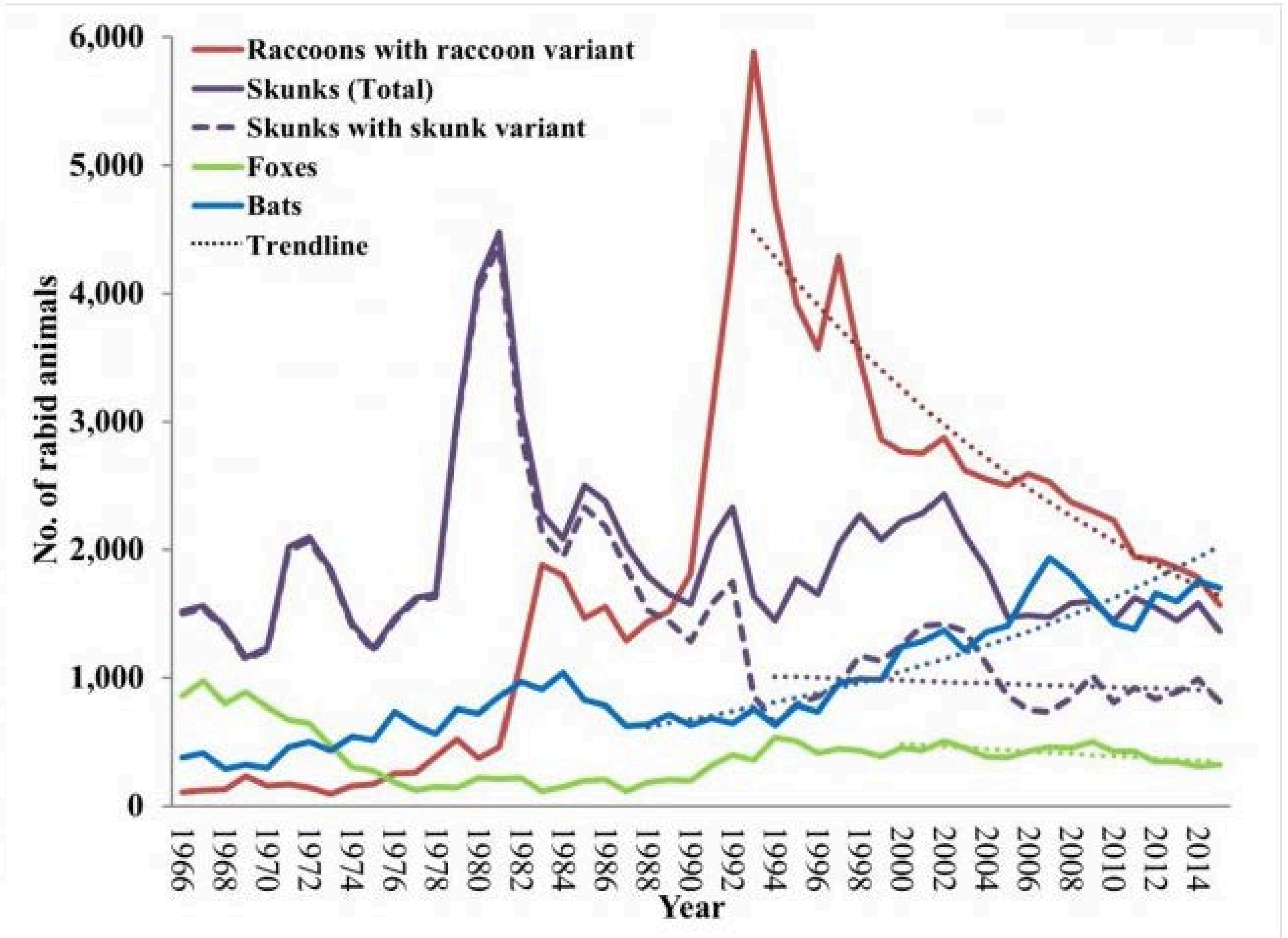
- Average of 3 cases a year (23 cases between 2008 and Sept 2017)
- Leading source are bats
- Transplant-related
    - 2004, four recipients from a donor who died of encephalitis in Texas
- No cases of human to human transmission

Cases of Rabies in humans in the US and Puerto Rico from 2011 to 2017

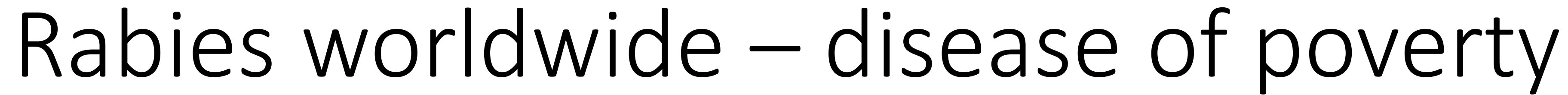
Date of onset	Date of death	Reporting state	Age (y)	Sex	Exposure*	Rabies virus variant†
5-May-17	21-May-17	VA	65	F	Bite	Dog, India
25-Nov-15	1-Dec-15	PR	54	M	Bite	Dog-mongoose, Caribbean
17-Sep-15	3-Oct-15	WY	77	F	Contact	Bat, Ln
30-Jul-15	24-Aug-15	MA	65	M	Bite, Philippines	Dog, Philippines
12-Sep-14	26-Sep-14	MO	52	M	Unknown	Bat, Ps
16-May-13	11-Jun-13	TX	28	M	Unknown, Guatemala	Dog, Guatemala
31-Jan-13	27-Feb-13	MD	49	M	Kidney transplant	Raccoon, eastern United States
6-Jul-12	31-Jul-12	CA	34	M	Bite	Bat,Tb
22-Dec-11	23-Jan-12	MA	63	M	Contact	Bat, My sp
3-Dec-11	19-Dec-11	SC	46	F	Unknown	Bat,Tb
1-Sep-11	14-Oct-11	MA	40	M	Contact, Brazil	Dog, Brazil
21-Aug-11	1-Sep-11	NC	20	M	Unknown (organ donor)§	Raccoon, eastern United States
14-Aug-11	31-Aug-11	NY	25	M	Contact, Afghanistan	Dog, Afghanistan
30-Jun-11	20-Jul-11	NJ	73	F	Bite, Haiti	Dog, Haiti
30-Apr-11	Survived	CA	8	F	Unknown	Unknown

https://www.cdc.gov/rabies/location/usa/surveillance/human_rabies.html





https://www.cdc.gov/rabies/location/usa/surveillance/wild_animals.html



Worldwide burden:

55,000 reported human cases, but vastly underreported

large burden in low- and middle-income countries

Mostly stray dogs

- About 20,000 cases in India each year
- About 10,000 cases in China each year, grossly under-reported

World Health Organization : Position paper on rabies vaccines. Wkly Epidemiol Rec 2007; 82: pp. 425-436

Association for the Prevention and Control of Rabies in India. Assessing the burden of rabies in India: a national multicentric survey. Progress report. Bhubaneswar, India: Association for the Prevention and Control of Rabies; 2003.

Bagcchi S. India fights rabies Lancet Infect Dis. 2015 Feb;15(2):156-7.