

Clinical Manifestations and Diagnosis

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CME Disclosure

- No financial conflicts of interest.

Case presentation

- 9yo girl presented in August with a 4-day history of frontal headache, nausea, and vomiting.
- Initially diagnosed with a viral syndrome by PCP.
- Over the next 24 hours, she had increased frontal headache, somnolence and emesis
- On day 8 of symptoms developed intermittent hallucinations, and increased agitation
- Pt became more lethargic at home, referred to the ED.
- Upon ED arrival, noted to be febrile, meningeal signs were subtle, but she has having agitation and altered sensorium.

Past Med Hx: Asthma

Past Surg Hx: none

Family Hx: HTN, DM

Immunizations: UTD

Social Hx:

- 4th grade
- Lives with parents and 2 siblings
- No pets/travel/sick contacts

Meds:

- Vancomycin
- Ceftriaxone

Allergies: amoxil (rash)

Any other questions you may want to ask?

Exposure History

- Sick contact
- Recent illness
- Substance exposure or abuse
- Travel
- Animal, insect including tick bites
- Water exposure

Water exposure

- Fresh water
 - Lakes
 - Rivers
 - Ponds
 - Hot springs
- Unchlorinated sources
 - Pools
 - Wells
 - Sprinklers

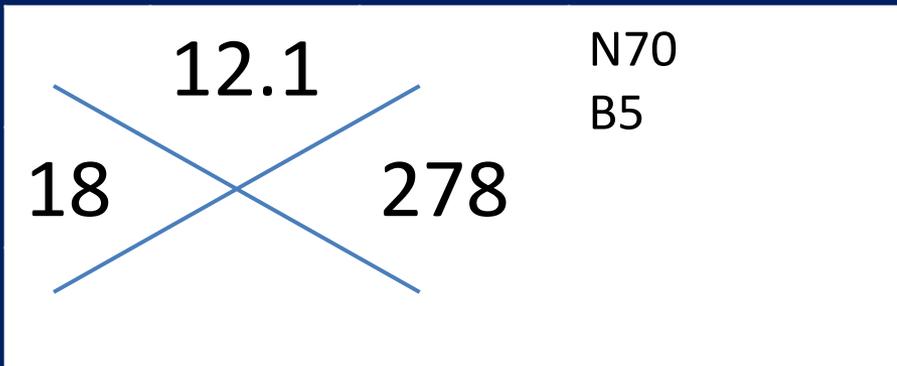
Physical exam

Tmin 95.5, Tc 98.2 HR: 76 RR: 28 BP: 106/73

- General: NAD, in bed, agitated, but with episodes of cooperation with exam
- HEENT: PERRL, MMM, oropharynx clear
- NECK: no lymphadenopathy. Pain on flexion; but full range of motion
- RESP: CTA bil.
- CVS: RRR, no murmur, no peripheral edema.
- ABD: NT/ND, +BS, no HSM.
- NEURO: CN II-XII grossly intact. No apparent focal deficit. Intermittent agitation, and hallucinations

- Evaluation was done with LP for CSF analysis (including cultures, enterovirus and HSV PCR), CBC with Diff, Blood cx.
- Admitted to the floor with the clinical diagnosis of meningoencephalitis.

Labs



- Na 137
- Cr 0.9
- AST 50, ALT 30
- Alb 4

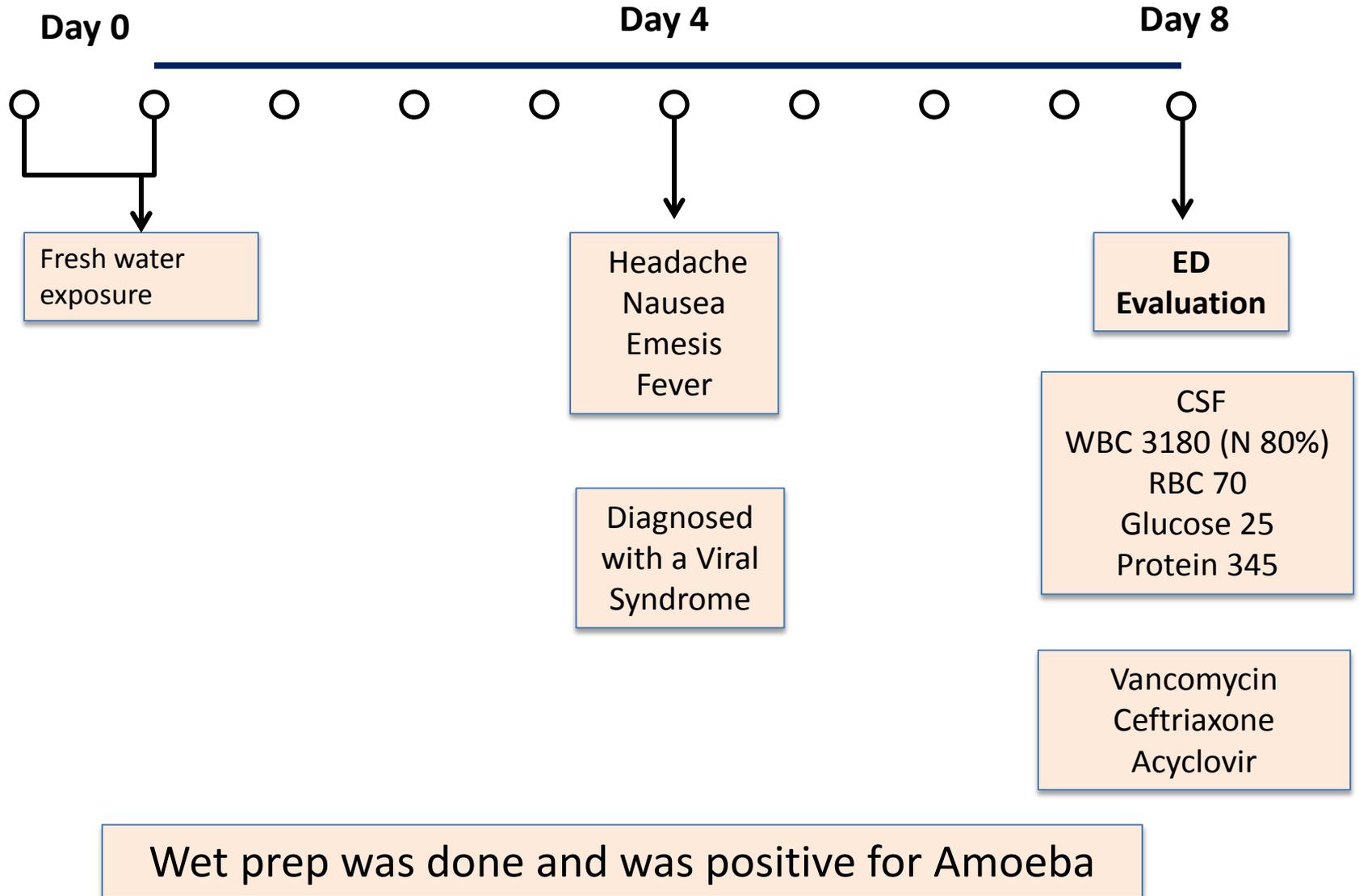
- CSF (LP): Opening pressure >55
WBC 3180 (N80), RBC 70
Glucose 25, Protein 345

She was started on Vancomycin, ceftriaxone and Acyclovir

Any suggestion for laboratory testing

- Wet prep
- Gram stain --- Pathology request to look for trophozoites
- Amoeba culture
- PCR

Summary of events



Encephalitis Overview

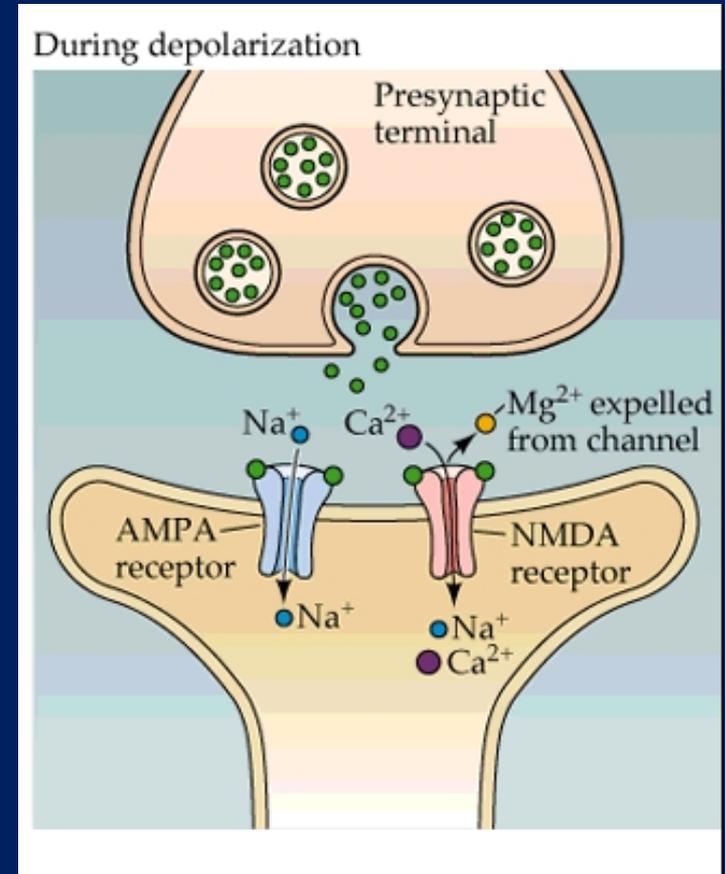
- Differential Diagnosis
- PAM presentation

General Causes

- Infections
 - Bacteria (Bartonella, Lyme, Mycoplasma)
 - Viruses (EV, HSV, arboviruses, rabies)
 - Fungi (Cryptococcus, Coccidioides)
 - Parasites (Naegleria, cysticercosis, malaria)
- Immune-mediated
 - Systemic inflammatory diseases: eg. SLE
 - Parainfectious: e.g. Mycoplasma, ADEM
 - Paraneoplastic: e.g. NMDA receptor antibodies

Anti-NMDAR Encephalitis

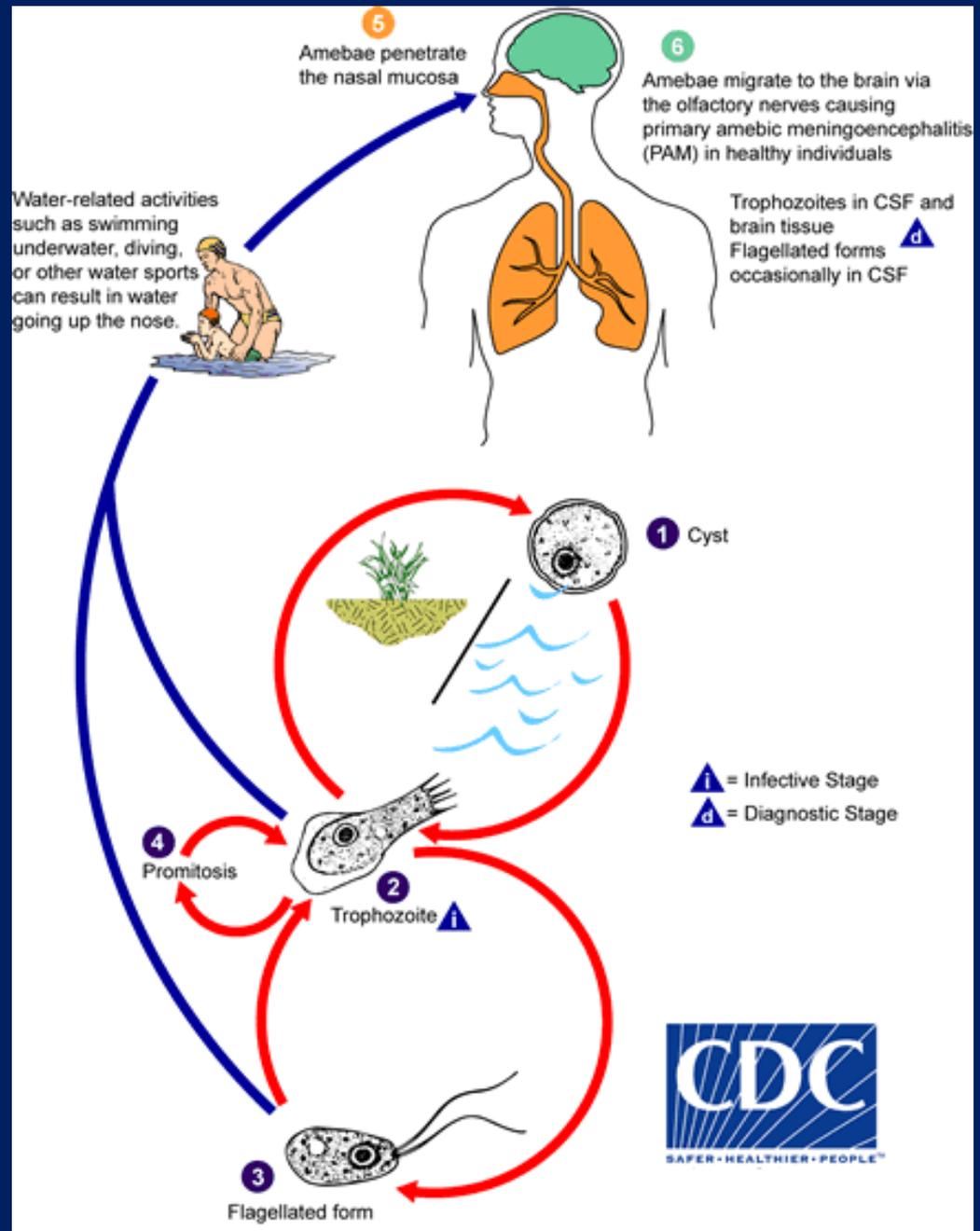
- N-Methyl-D-Aspartate receptor antibodies
- Described in 2007
- Median age 19 years
 - 40% children
- May occur with ovarian teratomas
- Common psychiatric and behavioral symptoms



Primary Amoebic Encephalitis

- *Naegleria fowleri*
- 1962-2013, 132 U.S. cases, 34 Florida cases
 - 4 survivors
 - 84% children <18, >75% males
- Acquired from freshwater lakes, rivers, hot springs, pools or tap water
 - Found in ½ of Florida lakes surveyed
 - Exists in lake bottom sediment
- Thrives in freshwater at $\geq 86^{\circ}\text{F}$, prefers 115°F
- Killed by drying and chlorine 1 ppm

Naegleria fowleri life cycle



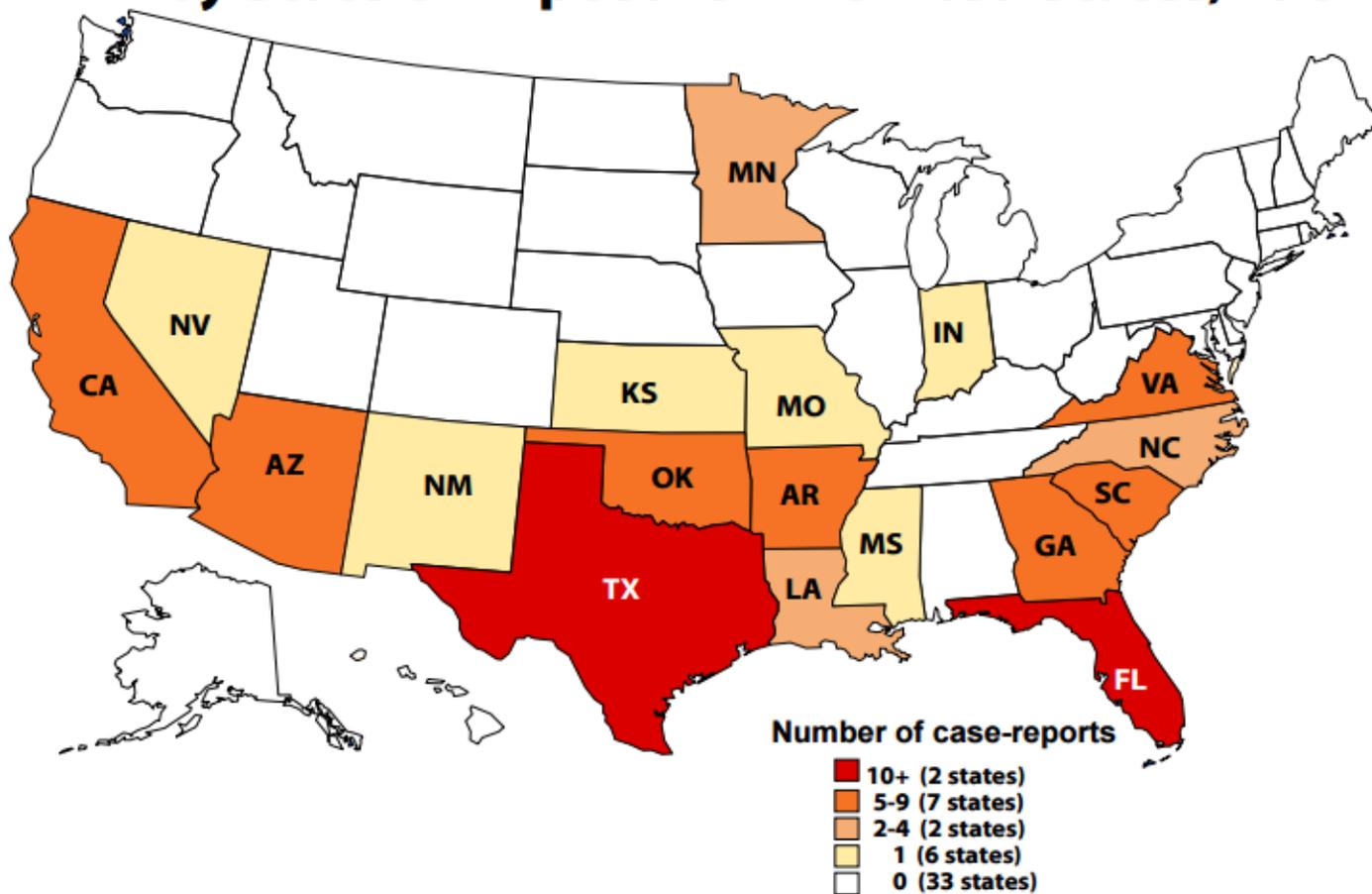
Primary Amoebic Encephalitis

- Incubation period: 1-5 days
- Symptoms: headache, fever, nausea, vomiting
 - Later stiff neck, mental status changes, seizures
- Death in about 5 days (1-12 days)

CSF Indices in PAM

- WBC count: 300-26,000/mm³
 - Mostly neutrophils
- RBC count: 0-24,600/mm³
- Protein: 100-1000 mg/dL
- Glucose: <10 mg/dL

Number of Case-reports of Primary Amebic Meningoencephalitis Caused by *Naegleria fowleri* (N=132) by State of Exposure*— United States, 1962–2013

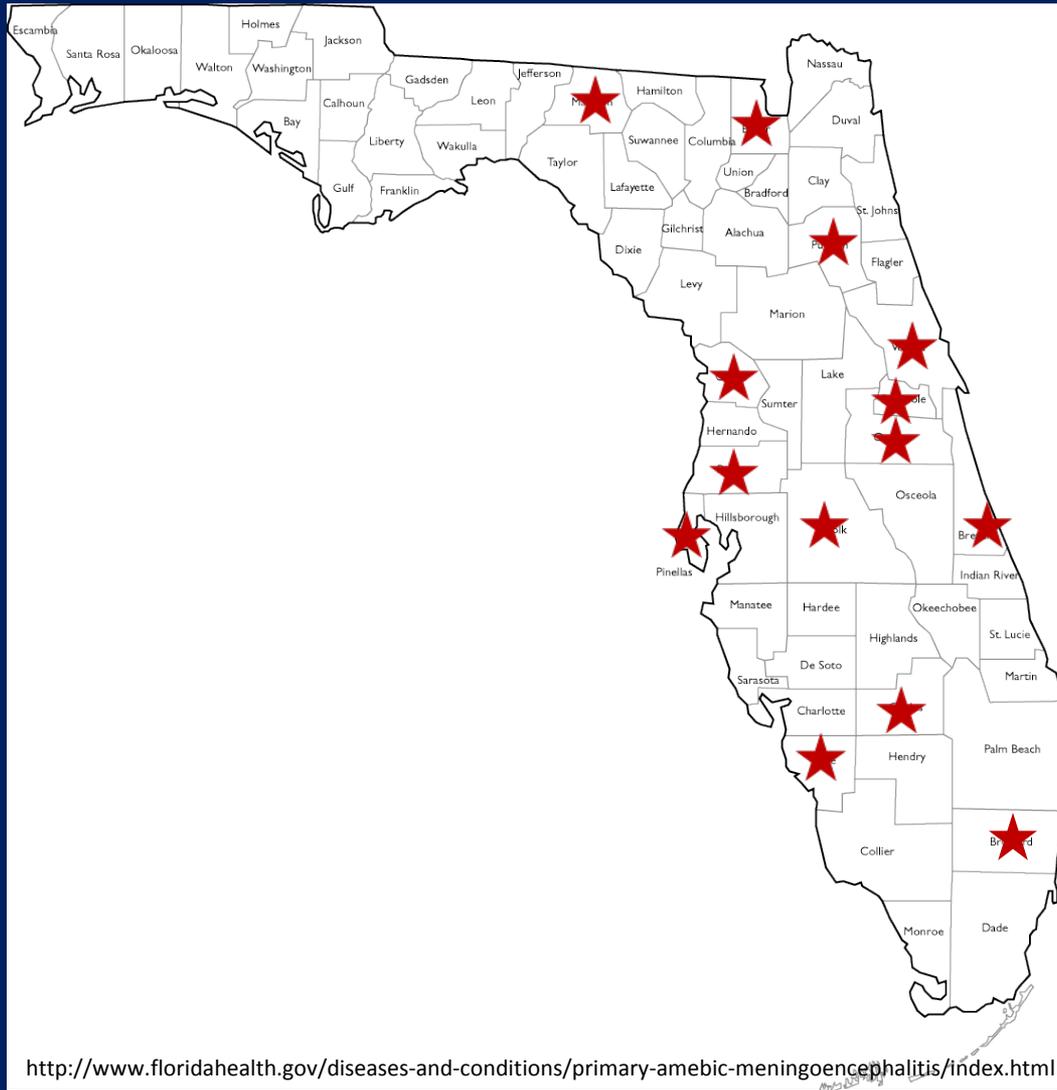


State (Abbreviation)	# of Cases
Arizona (AZ)	7
Arkansas (AR)	6
California (CA)	7
Florida (FL)	34
Georgia (GA)	5
Indiana	1
Kansas (KS)	1
Louisiana (LA)	4
Minnesota (MN)	2
Mississippi (MS)	1
Missouri (MO)	1
Nevada (NV)	1
New Mexico (NM)	1
North Carolina (NC)	4
Oklahoma (OK)	6
South Carolina (SC)	7
Texas (TX)	32
Virginia (VA)	7

- State of exposure unknown for 4 cases.
- Does not include one case from USVI.



Florida Cases of PAM, 1962-2013



Factors to Highlight Specific Etiologies

- Age
- Animal contact
- Insect contact
- Underlying or recent disease (medical or family history)
- Travel
- Recreational activities
- Vaccination status

Tunkel AR, et al. The management of encephalitis: clinical practice guidelines by the IDSA. Clin Infect Dis 2008;47:303-27.

Animal Contacts

- Bats: rabies virus, Nipah virus
- Cats: rabies virus, *Bartonella henselae*, *Coxiella burnetti*, *Toxoplasma gondii*
- Dogs: rabies virus
- Old world primates: herpes B virus
- Raccoons: rabies virus, *Baylisascaris procyonis*
- Rodents: lymphocytic choriomeningitis virus
- Sheep and goats: *Coxiella burnetti*
- Skunks: rabies virus

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Insect Contacts

- Mosquitos: WNV and other arboviruses, malaria, Japanese encephalitis virus
- Ticks: tickborne encephalitis virus, *Bartonella henselae*, ehrlichiosis, *Rickettsia rickettsiae*, *Borellia burgdorferi*

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Underlying Disease

- Agammaglobulinemia: enteroviruses, *Mycoplasma pneumoniae*
- Other immunocompromised: HSV, CMV, EBV, VZV, WNV, Toxoplasma, M. tuberculosis, fungal infections
- Recent illness or vaccination: ADEM (acute disseminated encephalomyelitis)

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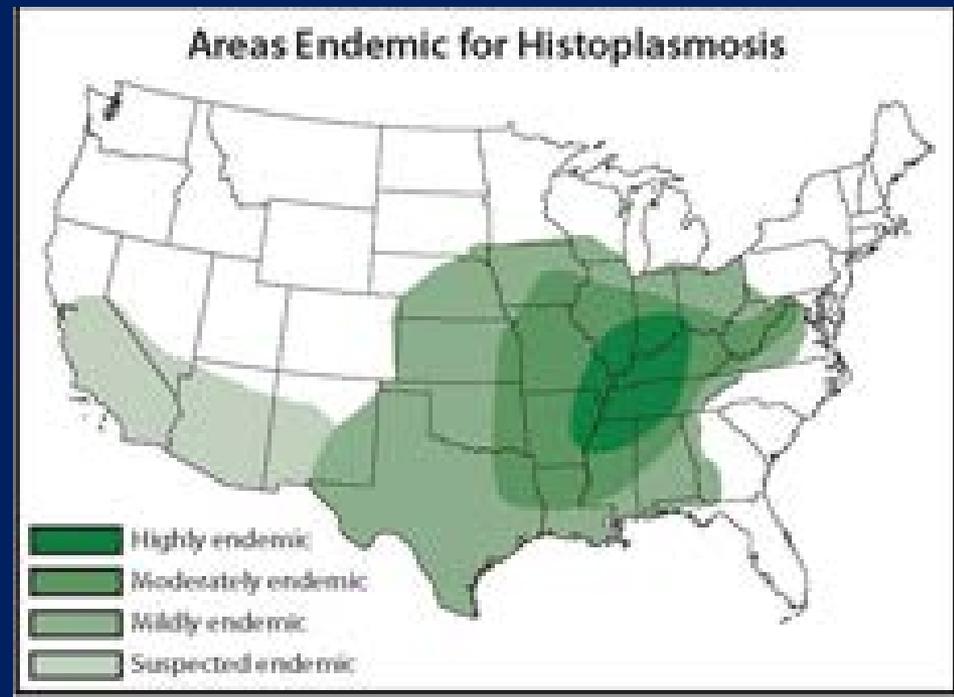
International Travel

- Africa: rabies, WNV, malaria, trypanosomiasis
- Australia: Murray Valley encephalitis virus, Japanese encephalitis virus, Hendra virus
- Central and South America: rabies, arboviruses, malaria, RMSF, cysticercosis
- Europe: WNV, tickborne encephalitis virus, Anaplasma phagocytophila, Lyme disease
- India, Nepal: rabies, Japanese encephalitis virus, malaria
- Middle East: WNV, malaria
- Russia: tickborne encephalitis virus
- SE Asia, China, Pacific Rim: Japanese encephalitis virus, tickborne encephalitis virus, Nipah virus, malaria, cysticercosis

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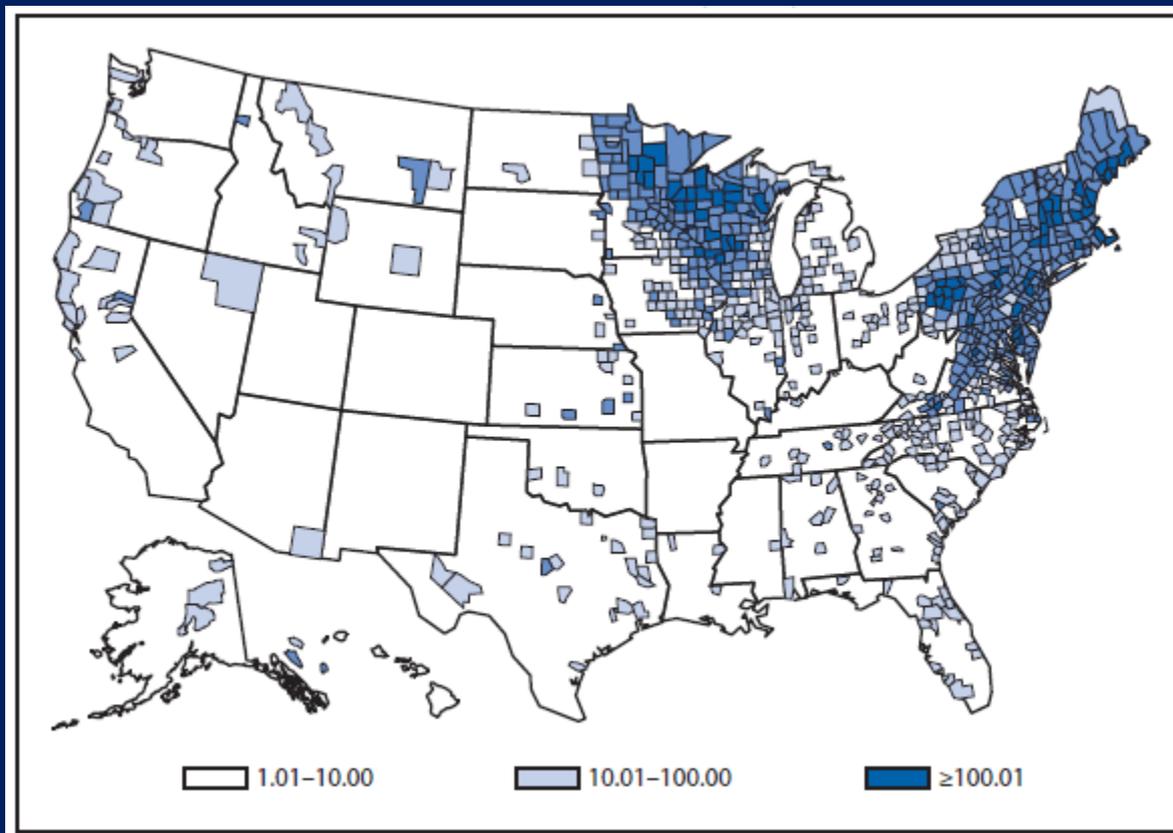
Domestic Travel

- Ohio & Mississippi river valleys: blastomycosis and histoplasmosis



Domestic Travel

- Northeastern, upper Midwest: Lyme disease

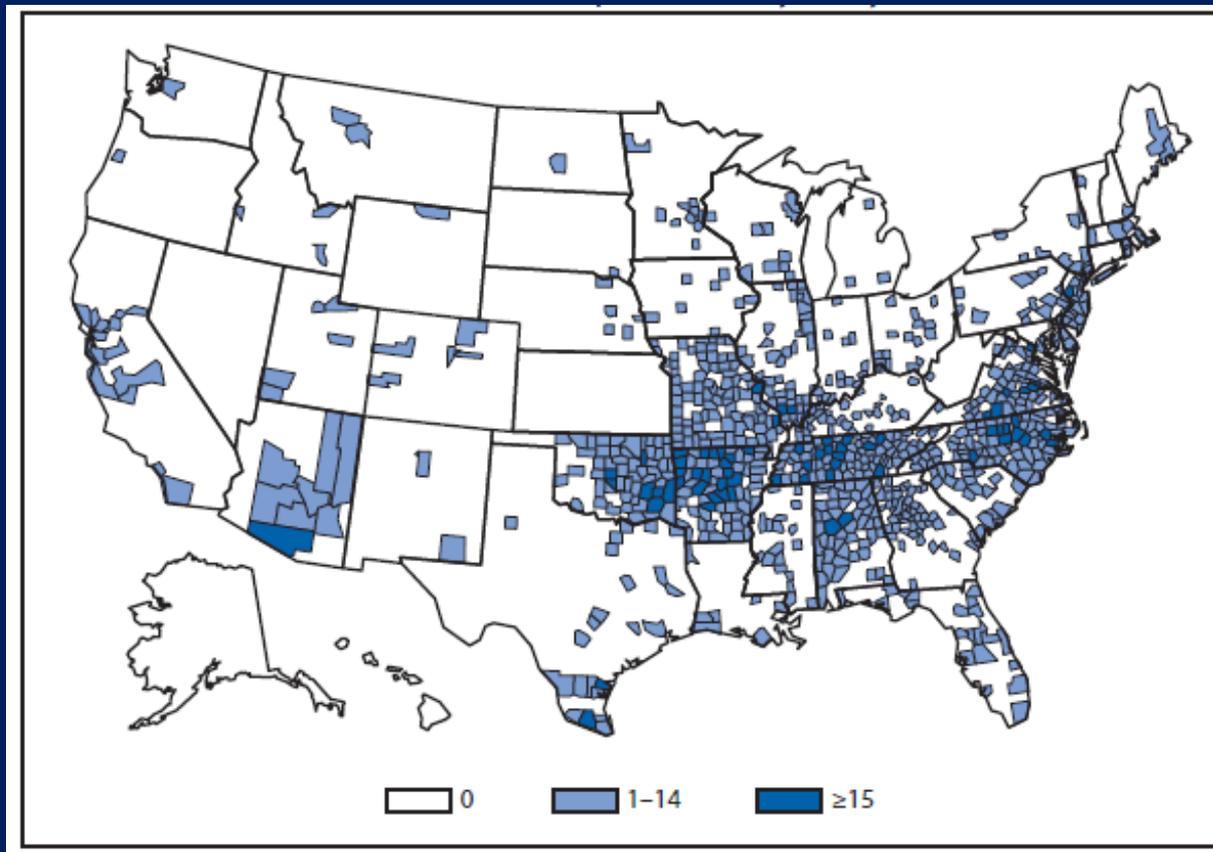


Incidence per 100,000
By county, 2012

CDC. MMWR 2014;
61(53)1-121.

Domestic Travel

- Central Atlantic: RMSF

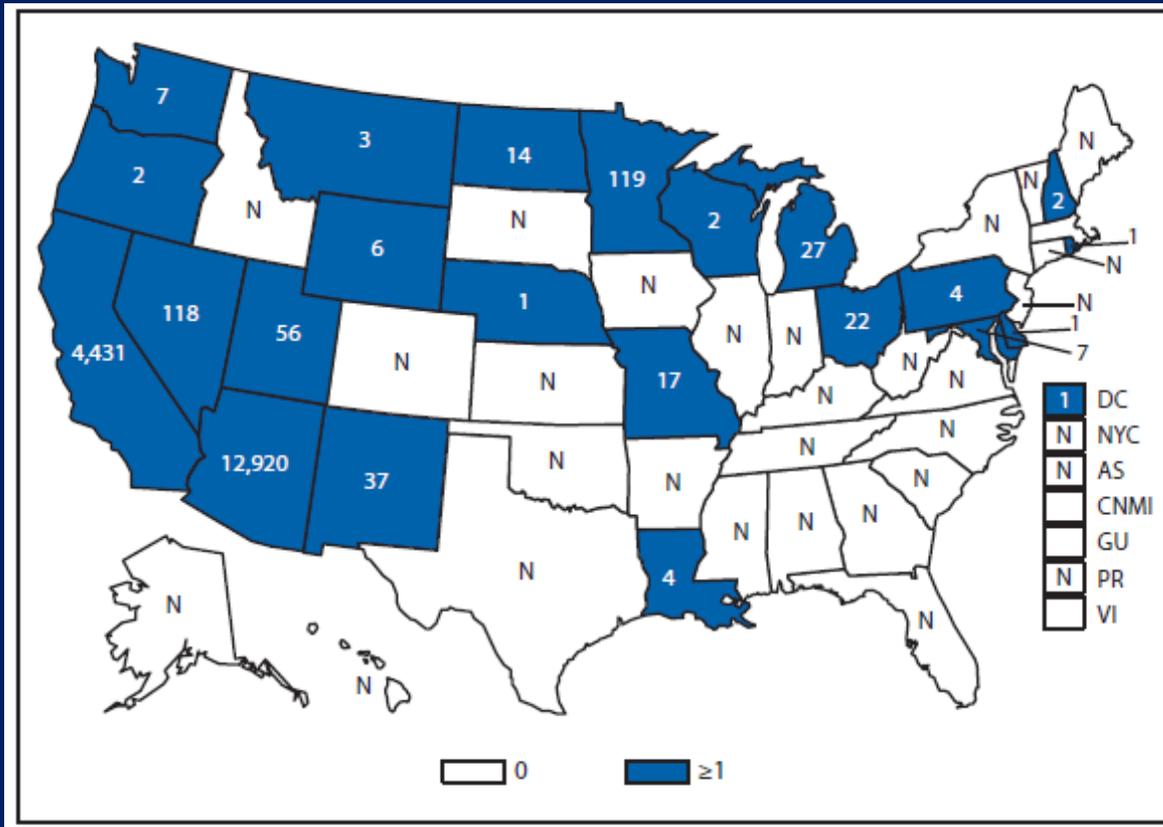


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Domestic Travel

- Desert southwestern states: Coccidioidomycosis



73% in Arizona, 25% in California

Recreational Activities

- Camping/hunting: all mosquito or tick related infections
- Sexual contact: HIV, syphilis
- Spelunking: rabies, *Histoplasma capsulatum*
- Swimming in fresh water: enteroviruses, *Naegleria fowleri*

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Unvaccinated Status

- *Bordetella pertussis*
- *Haemophilus influenzae b*
- Influenza virus
- Japanese encephalitis virus
- Measles
- Mumps
- *Neisseria meningitidis*
- Rubella
- *Streptococcus pneumoniae*
- Varicella zoster virus

Encephalitis Management

- Supportive care: manage seizures, cerebral edema, septic shock, SIADH
- Brain MRI with and without contrast preferred
- EEG as indicated
- Empiric therapy for specific pathogens: antibacterials, acyclovir, PAM therapy
- Steroids, IVIG for postinfectious forms
 - ADEM, NMDAR encephalitis

Specific Laboratory Diagnosis

Cerebrospinal Fluid

- Polymerase chain reaction (PCR) for HSV and enteroviruses
- PCR for parechovirus in infants
- As indicated:
 - PCR for VZV, HHV-6
 - India ink & cryptococcal antigen, measles antibody
 - Wet mount or Wright-Giemsa stain for amoebae
- Get extra CSF and save it!

Specific Laboratory Diagnosis

Nasopharyngeal wash or swab

- Enteroviruses
- *Mycoplasma pneumoniae*
- Adenovirus
- RSV
- Influenza A & B

Specific Laboratory Diagnosis

Acute phase serum

- *Mycoplasma pneumoniae*
- Arboviruses
- NMDA receptor antibodies
- EBV
- Parvovirus B19
- Measles
- Additional as indicated by history

Conclusions

- Ask the right questions to narrow the huge differential diagnosis.
 - Animal contacts
 - Insect contacts
 - Travel
 - Recreational activities
 - Immunization status
- Get enough CSF for extra testing.
- Order the correct tests.
- Start empiric therapies early.

Questions

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