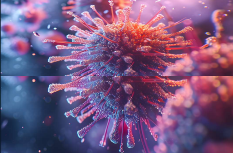



47 Encephalitis including West Nile and Rabies
Speaker: Allan Tunkel, MD, PhD, MACP



Encephalitis Including West Nile and Rabies

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7/12/2025

1



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Encephalitis Definitions

3

- Encephalitis
 - ▣ Inflammation of brain parenchyma with neurologic dysfunction
 - ▣ Gold standard is pathologic examination and testing of brain tissue
 - ▣ Usually based on clinical, laboratory, and imaging
- Encephalopathy
 - ▣ Altered consciousness (confusion, disorientation, behavioral changes, cognitive impairment) \pm inflammation
 - ▣ Usually metabolic or toxic conditions

3

Encephalitis Epidemiology

4

- ~5 cases/100,000 population annually in US from 1990-2017
- >1 million cases annually worldwide
 - ▣ Rabies
 - ▣ Measles
 - ▣ Japanese encephalitis virus

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Encephalitis

Etiology

- California Encephalitis Project (CEP) reviewed 1,570 cases over 7-year period (CID 2006;43:1565)
- Confirmed or probable etiology in 16%
 - 69% viral
 - 20% bacterial
 - 7% prion
 - 3% parasitic
 - 1% fungal
- Possible etiology in 13%

5

Encephalitis

Etiology

- Australian Childhood Encephalitis Study (CID 2020;70:2517)
- 287 children with confirmed encephalitis
- 57% infectious (confirmed/probable)
- 25% immune-mediated
- 17% unknown

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Reasons Etiology not Identified

- Undiscovered pathogens
- Uncommon presentation by common pathogens
- Common presentation by uncommon pathogens
- Wrong test
- Wrong sample
- Wrong timing
- Not an infection

7

General Approach

- Can't test for everything
- Epidemiologic and clinical clues
- General diagnostic studies
- Neuroimaging clues
- Consider noninfectious etiologies

Tunkel et al. Clin Infect Dis 2008;47:303
Venkatesan et al. Clin Infect Dis 2013;57:1114
Bloch et al. Clin Infect Dis 2023;doi.org/10.1093/cid/ciad306

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47 Encephalitis including West Nile and Rabies

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Question #1

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- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101°F; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm³ (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative

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Question #1

10

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

10

Question #1

11

What is the next step in the management of this patient?

- A. Perform a brain biopsy of the left temporal lobe
- B. Obtain new CSF for HSV PCR testing
- C. Send serum for HSV IgG antibodies
- D. Repeat brain MRI
- E. Discontinue acyclovir

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Question #1

12

What is the next step in the management of this patient?

- A. Perform a brain biopsy of the left temporal lobe
- B. Obtain new CSF for HSV PCR testing *
- C. Send serum for HSV IgG antibodies
- D. Repeat brain MRI
- E. Discontinue acyclovir

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Question #1

- Repeat CSF analysis on day #4 reveals that the PCR is now positive for HSV-1
- The patient continues to improve and completes a 14-day course of acyclovir
- One month later, he presents again with fever and confusion
- CSF analysis reveals a WBC count of 30/mm³ (all lymphocytes) with normal glucose and mildly elevated protein; CSF PCR tests for HSV-1 and HSV-2 are negative

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Question #2

- Which of the following is the most likely reason for his second presentation of encephalitis?
- A. Relapse of herpes simplex encephalitis
 - B. Development of acyclovir-resistant herpes simplex encephalitis
 - C. Development of autoimmune encephalitis
 - D. Acyclovir neurotoxicity

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Question #2

- Which of the following is the most likely reason for his second presentation of encephalitis?
- A. Relapse of herpes simplex encephalitis
 - B. Development of acyclovir-resistant herpes simplex encephalitis
 - C. Development of autoimmune encephalitis *
 - D. Acyclovir neurotoxicity

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Herpes Simplex Encephalitis

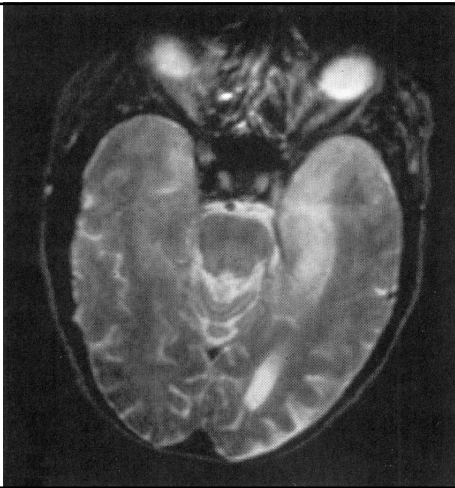
- Epidemiology
 - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
 - Accounts for 10-20% of encephalitis viral infections
 - Occurs throughout the year and in patients of all ages
 - Described following whole brain irradiation or following a neurosurgical procedure
 - Majority in adults caused by HSV-1
- Clinical features
 - Fever, personality change, dysphasia, autonomic dysfunction

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Herpes Simplex Encephalitis

- Electroencephalography
 - ▢ Sensitivity of ~84%
 - ▢ Periodic lateralizing epileptiform discharges (PLEDs)
- Neuroimaging
 - ▢ Computed tomography (lesions in 50-75% of patients)
 - ▢ Magnetic resonance imaging (>90% of cases)
- Brain biopsy
 - ▢ Inflammation with widespread hemorrhagic necrosis
 - ▢ Intranuclear inclusions (50% of patients)
 - ▢ Reserve for patients not responding to acyclovir therapy

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Herpes Simplex Encephalitis

- Cerebrospinal fluid (CSF) findings
 - ▢ Lymphocytic pleocytosis (mean of 100 cells/mm³)
 - ▢ Presence of red blood cells (25% never have RBCs)
 - ▢ Elevated protein
 - ▢ Absent pleocytosis (<5/mm³) in up to 25% of patients on initial evaluation*
- CSF Polymerase Chain Reaction
 - ▢ Sensitivity 98%
 - ▢ Specificity 94%
 - ▢ Positive predictive value 95%
 - ▢ Negative predictive value 98%
 - ▢ If negative, may need new CSF sample in 3-7 days

*Habis et al. Clin Infect Dis 2024;doi.org/10.1093/cid/ciae391

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Herpes Simplex Encephalitis

- Acyclovir is the antiviral agent of choice
 - ▢ Mortality of 19% at 6 months
 - ▢ Mortality of 28% at 18 months
 - ▢ Morbidity ~50%
- Dosage in adults is 30 mg/kg/day in 3 divided dosages (in those with normal renal function) for 14-21 days
- No added benefit on oral valacyclovir (3-month course) after standard course of acyclovir

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Other Herpesviruses

21

- Varicella-zoster virus
 - Can occur without rash (zoster sine herpete)
 - Focal neurologic deficits and seizures
 - CSF PCR; lower sensitivity in those with vasculopathy so also check CSF antibodies
 - MRI/MRA large vessel vasculitis and ischemia
 - Acyclovir (however, no controlled studies) + ?corticosteroids (if vasculopathy)
- Epstein-Barr virus
 - Encephalitis and/or transverse myelitis
 - Serologic testing; CSF PCR (may have false-positives)

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Other Herpesviruses

22

- Human herpesvirus 6
 - Immunocompromised patients, but seen in children
 - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
 - Ganciclovir or foscarnet
- Cytomegalovirus
 - Immunocompromised (especially HIV)
 - Evidence of widespread disease
 - CSF PCR (sensitivity 82-100%; specificity 86-100%)
 - MRI may reveal subependymal gadolinium enhancement and non-specific white matter changes
 - Ganciclovir + foscarnet

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Question #3

23

- 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused
- He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

23

Question #3

24

- T 103.1°F, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

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Question #3

Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

- A. Serum IgM
- B. Serum polymerase chain reaction
- C. Cerebrospinal fluid IgM
- D. Cerebrospinal fluid polymerase chain reaction
- E. Brain MRI

25

Question #3

Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

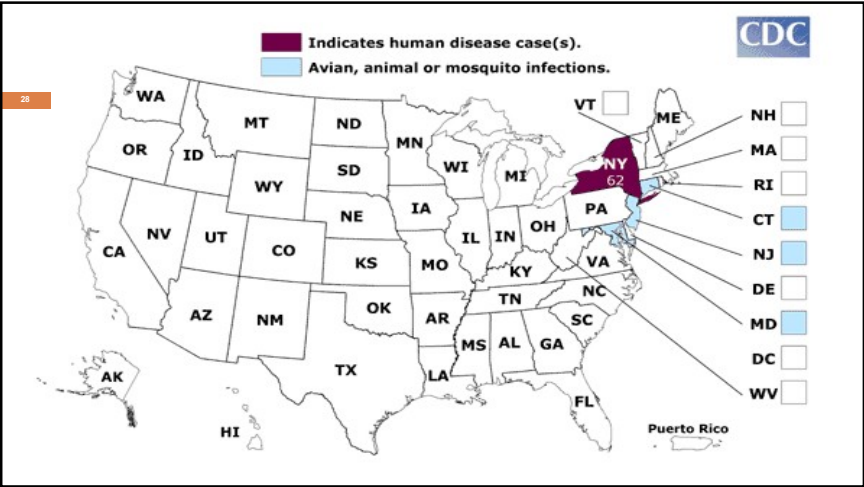
- A. Serum IgM
- B. Serum polymerase chain reaction
- C. Cerebrospinal fluid IgM *
- D. Cerebrospinal fluid polymerase chain reaction
- E. Brain MRI

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West Nile Virus (WNV) Encephalitis

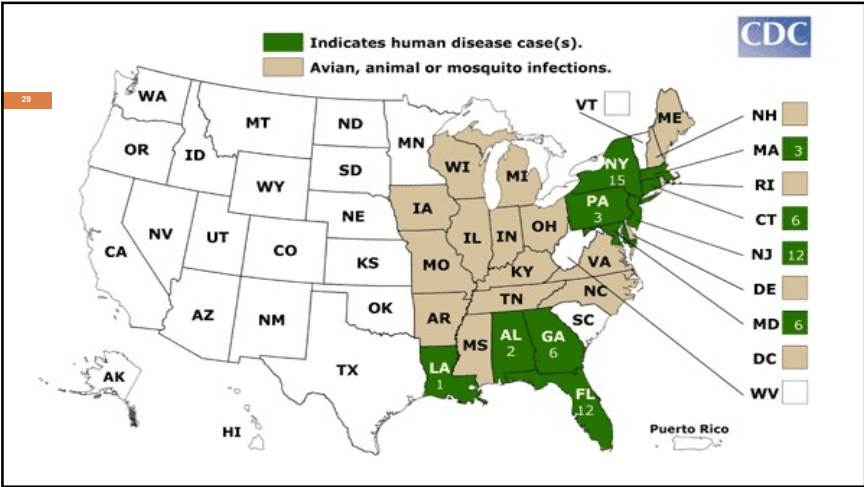
- First US cases reported in 1999 in New York City
- Birds are main reservoirs
- Mosquito vector
- Other modes of transmission
 - ▣ Transplanted organs
 - ▣ Blood transfusions
 - ▣ Breast milk
 - ▣ Transplacental
 - ▣ Occupational

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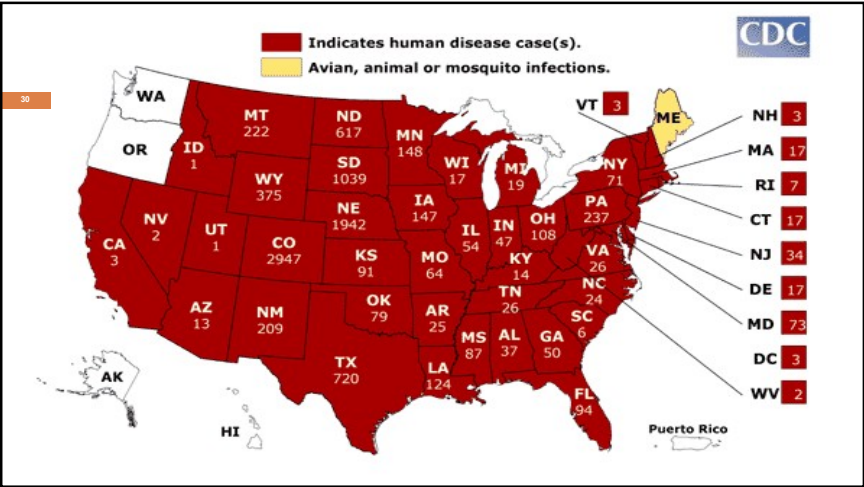


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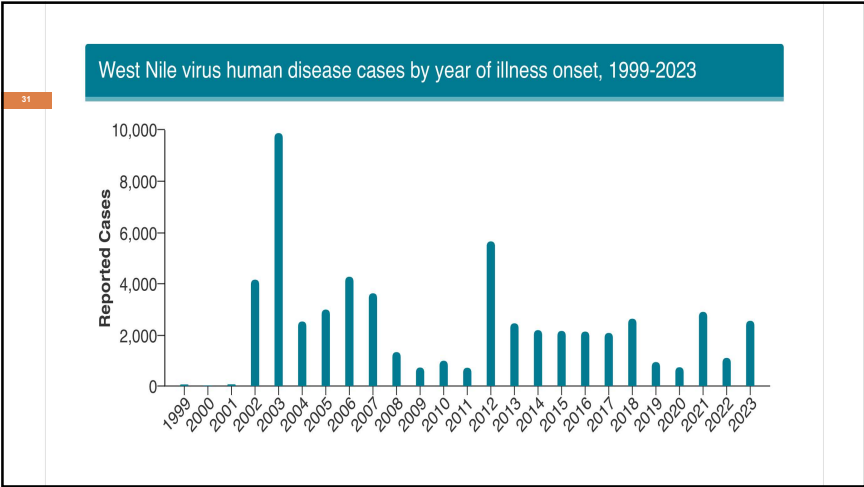
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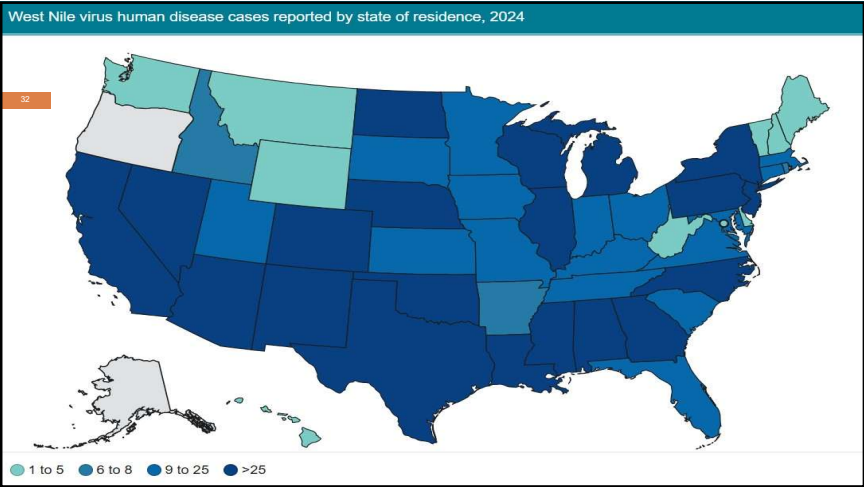
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West Nile Virus Clinical Syndromes

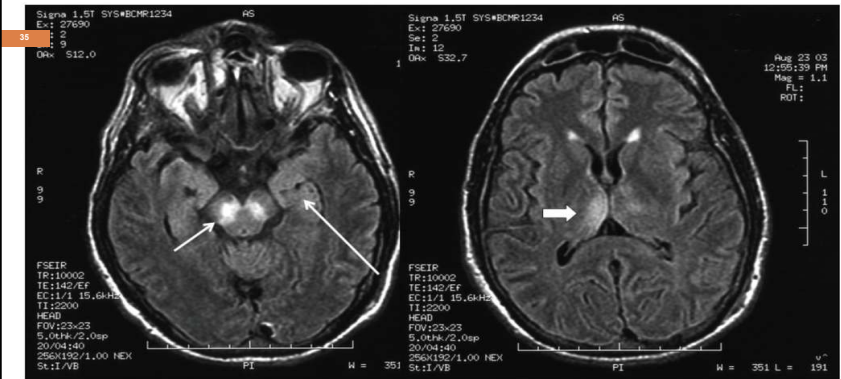
- No clinical illness or symptoms (~80%)
- West Nile Fever (~20%)
- Severe WNV Disease (1 in 150)
 - ▣ Meningitis (37%)
 - ▣ Encephalitis/Meningoencephalitis (53%)
 - ▣ Poliomyelitis-like flaccid paralysis (7%)

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West Nile Virus Encephalitis

- Diagnosis
 - ▣ Serum IgM antibody (8-14 days of illness onset)
 - ▣ CSF reveals lymphocytic pleocytosis and elevated protein; glucose is normal
 - ▣ CSF IgM (positive in >90%)
 - ▣ CSF PCR (<60% sensitivity)
 - ▣ Neuroimaging

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West Nile Virus Encephalitis

- Therapy
 - ▣ Supportive
 - ▣ Ribavirin, interferon alpha, and IVIG don't work

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Other Arboviruses

- St. Louis encephalitis virus
 - ▢ Mosquito vector; bird reservoir
 - ▢ Endemic in western US; periodic outbreaks in eastern US
 - ▢ Urinary symptoms early; SIADH (one-third of cases)
 - ▢ Serology; CSF IgM
- Japanese encephalitis virus
 - ▢ Most common cause of mosquito-borne encephalitis worldwide (SE Asia, China, India, Nepal, Korea, Japan)
 - ▢ Mainly children; rice fields where vectors breed
 - ▢ Seizures and parkinsonian features; poliomyelitis-like flaccid paralysis
 - ▢ Serology; CSF IgM

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Other Arboviruses

- Powassan virus
 - ▢ Tick vector (Ixodes scapularis in NE); rodent reservoir; New England
 - ▢ Prevalence among animal hosts and vectors increasing
 - ▢ Parkinsonism, involvement of basal ganglia and thalamus common
 - ▢ Serology; CSF IgM; metagenomic sequencing
- Tickborne encephalitis virus
 - ▢ Tick vector, rodent reservoir; drinking unpasteurized milk or cheese; solid organ transplantation; rituximab
 - ▢ Eastern Russia, central Europe
 - ▢ Poliomyelitis-like paralysis
 - ▢ Serology; CSF IgM
 - ▢ Anti-TBE immune globulin for post-exposure prophylaxis

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Other Arboviruses

- La Crosse virus
 - ▢ Mosquito vector; chipmunk and squirrel reservoir
 - ▢ Midwest and eastern US; woodlands
 - ▢ 2nd most common arbovirus in US
 - ▢ Serology; CSF IgM; SIADH (~20%)
- Eastern equine encephalitis virus
 - ▢ Mosquito vector; bird reservoir in North America; organ transplantation
 - ▢ Primarily Atlantic and Gulf coast states
 - ▢ Abrupt onset with fulminant course; seizures common
 - ▢ High case-fatality rate (50-70%)
 - ▢ Serologic testing
 - ▢ High CSF WBC count (>1000 cells/mm³)

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40

Measles Virus

- Primary encephalitis
 - ▢ Up to 1 per 1,000 infections
 - ▢ Usually appears within a few days (typically 5 days) of rash
 - ▢ Fever, headache, stiff neck, drowsiness, convulsions, coma
 - ▢ Rapidly progressive and fatal in ~15%
- Acute disseminated encephalomyelitis
 - ▢ Up to 1 per 1000 infections
 - ▢ Usually appears ~2 weeks after exposure
 - ▢ Demyelinating disease; post-infectious autoimmune response
 - ▢ Fever, fatigue, headache, nausea, vomiting
 - ▢ 10-20% mortality

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Measles Virus

- 41 Inclusion body encephalitis
 - Unvaccinated children and adults; immunocompromised
 - Symptoms 1-6 months after exposure;
 - Decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
 - Acquisition of measles before 2 years of age
 - 6-10 years after infection (range 3-35 years)
 - Behavioral changes, cognitive impairment at presentation
 - Myoclonus, seizures, neurologic deterioration (coma and death) later

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Meningitis/Encephalitis Panel

Bacteria	Viruses	Fungi
<i>Escherichia coli</i> K1	Cytomegalovirus	<i>Cryptococcus neoformans/gatti</i>
<i>Haemophilus influenzae</i>	Enterovirus	
<i>Listeria monocytogenes</i>	Herpes simplex virus 1	
<i>Neisseria meningitidis</i>	Herpes simplex virus 2	
<i>Streptococcus agalactiae</i>	Human herpesvirus 6	
<i>Streptococcus pneumoniae</i>	Human parechovirus	
	Varicella zoster virus	

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Metagenomic Next-generation Sequencing

- Allows unbiased or agnostic pan-species molecular diagnostics
- 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing*
- 220 CNS infections, 40% identified by conventional methods and NGS, 22% by NGS alone and 36% only by conventional methods**
- Possible role in testing of enigmatic cases

*Wilson et al. NEJM 2019;380:2327

**Benoit et al. Nature Med 2024;30:3522

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Question #4

- 44 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk
- Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity
- You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster
- He has never been vaccinated against rabies

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Question #4

In addition to administration of rabies vaccine, what is the most appropriate management?

- A. Rabies immune globulin at the bite site
- B. Rabies immune globulin in the deltoid muscle
- C. Rabies immune globulin in the buttocks
- D. Rabies immune globulin intraperitoneally
- E. Nothing further is indicated

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Question #4

In addition to administration of rabies vaccine, what is the most appropriate management?

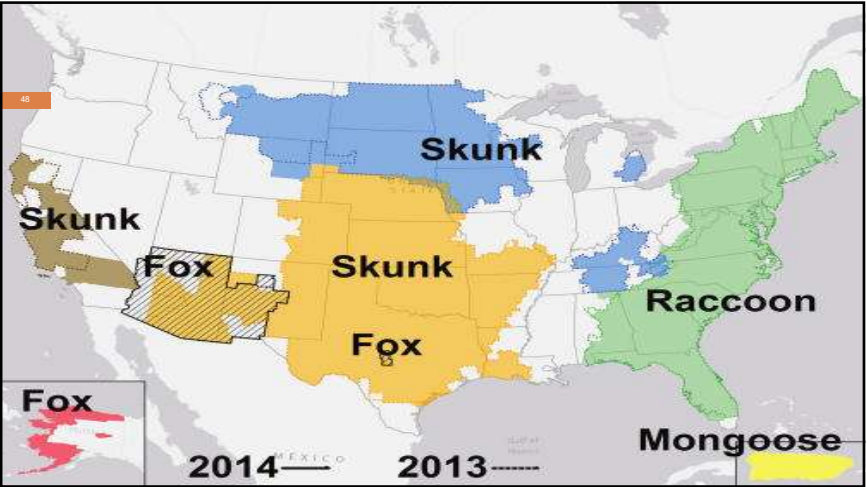
- A. Rabies immune globulin at the bite site *
- B. Rabies immune globulin in the deltoid muscle
- C. Rabies immune globulin in the buttocks
- D. Rabies immune globulin intraperitoneally
- E. Nothing further is indicated

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Rabies

- Transmitted by bite of infected animal
 - Dogs are principal vector (98% of cases) worldwide
 - May be transmitted after unrecognized bites by bats
- Rare and sporadic in US – 125 cases from 1960-2018
 - 36 (28%) attributed to dog bite during international travel
 - 89 acquired in US; 62 (70%) attributed to bats
- Worldwide in distribution (50,000-100,000 annual deaths)
- Incubation period 20-90 days

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Rabies

- 48
 - Encephalitic (furious) form (80%)
 - ▣ Agitation alternating with lucidity
 - ▣ Hypersalivation
 - ▣ Hydrophobia
 - ▣ Bizarre behavior
 - ▣ Disorientation, stupor, coma, death
 - Paralytic (dumb) form
 - ▣ Ascending paralysis; early muscle weakness
 - ▣ Later cerebral involvement

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Rabies

- 50
 - Diagnosis
 - ▣ Culture and RT-PCR of saliva
 - ▣ Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
 - ▣ CSF antibodies and RT-PCR
 - ▣ Brain biopsy (antigen detection/Negri bodies)
 - Therapy
 - ▣ Supportive
 - ▣ Milwaukee Protocol has failed in 26 cases
 - ▣ Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

50

Question #5

- 51
 - 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations
 - On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face
 - CSF analysis reveals a WBC count of 20/mm³, with normal glucose and protein
 - Brain MRI is normal

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Question #5

- 52
 - EEG reveals diffuse slowing
 - CSF Gram stain and cultures, and PCR for HSV are negative
 - A diagnosis of autoimmune encephalitis is considered, and appropriate studies sent
 - CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor
 - Corticosteroids and IV immune globulin are initiated

52

Question #5

Which of the following studies should now be performed?

- A. CT scan of the chest
- B. CT scan of the abdomen
- C. Carotid ultrasound
- D. Renal ultrasound
- E. Transvaginal ultrasound

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Question #5

Which of the following studies should now be performed?

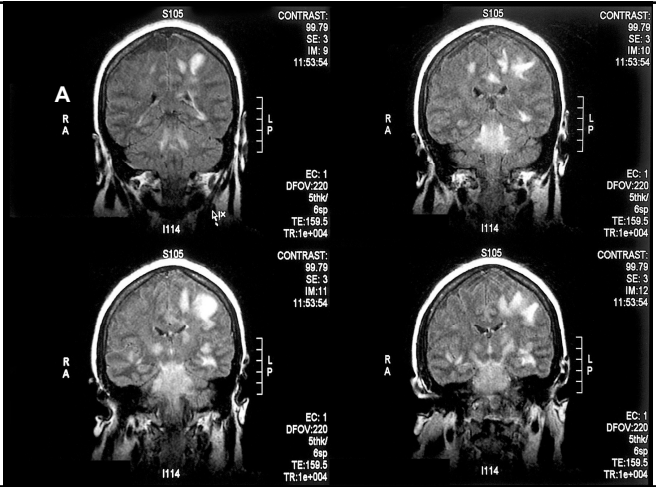
- A. CT scan of the chest
- B. CT scan of the abdomen
- C. Carotid ultrasound
- D. Renal ultrasound
- E. Transvaginal ultrasound *

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Encephalitis
Noninfectious Etiologies

- Acute disseminated encephalomyelitis (ADEM)
 - ▢ 10-15% of encephalitis cases in US
 - ▢ Post-infectious
 - ▢ Symptoms 2-4 weeks after trigger
 - ▢ MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
- Approximately 20-30% of encephalitis cases are due to autoimmune conditions (e.g., anti-N-methyl-D-aspartate receptor [Anti-NMDAR] encephalitis)

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Anti-NMDAR Encephalitis

57

- Neuronal antibody-associated encephalitis
- In California Encephalitis Project, this entity exceeded that of any single viral entity in children and was also seen in adults
- Female to male ratio of about 8:2
- 37% of patients younger than 18 years at presentation

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Anti-NMDAR Encephalitis

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- Abnormal behavior (psychiatric symptoms)
- Cognitive dysfunction
- Seizures
- Movement disorders (orofacial dyskinesias)
- Decreased level of consciousness
- Autonomic instability
- May be associated with ovarian teratoma (in ~50% of patients older than 18 years)

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Anti-NMDAR Encephalitis

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- CSF analysis
 - Mild pleocytosis (median WBC 23/mm³); normal glucose and protein
 - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF and serum
 - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies*

*Armangue et al. Brain 2023;146:4306

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Anti-NMDAR Encephalitis

60

- Neuroimaging
 - Abnormal in 50%, but nonspecific
 - T2 and FLAIR hyperintensity (hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG
 - Diffuse or focal slowing
 - Occasional superimposed epileptic activity

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Anti-NMDAR Encephalitis

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- Therapy
 - ▣ First-line
 - Corticosteroids
 - Intravenous immunoglobulin
 - Plasma exchange
 - ▣ Second-line
 - Rituximab or cyclophosphamide
 - ▣ Female patients should be evaluated for ovarian teratoma; if present, remove
- 75% of patients have mild sequelae or fully recover; relapse in up to 24%

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QUESTIONS

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