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CNS Infections, Part 1 and Part 2

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CNS Infections: Meningitis & Encephalitis

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Goals

- Review the clinical presentation, diagnosis, treatment, and complications of the following viral causes of CNS infections:
- Bacterial meningitis
- TB meningitis
- Viral meningitis
- Herpes Simplex Encephalitis
- HIV and CNS infections
- Rabies

What *is* the difference between “encephalitis” and “meningitis,” anyway?

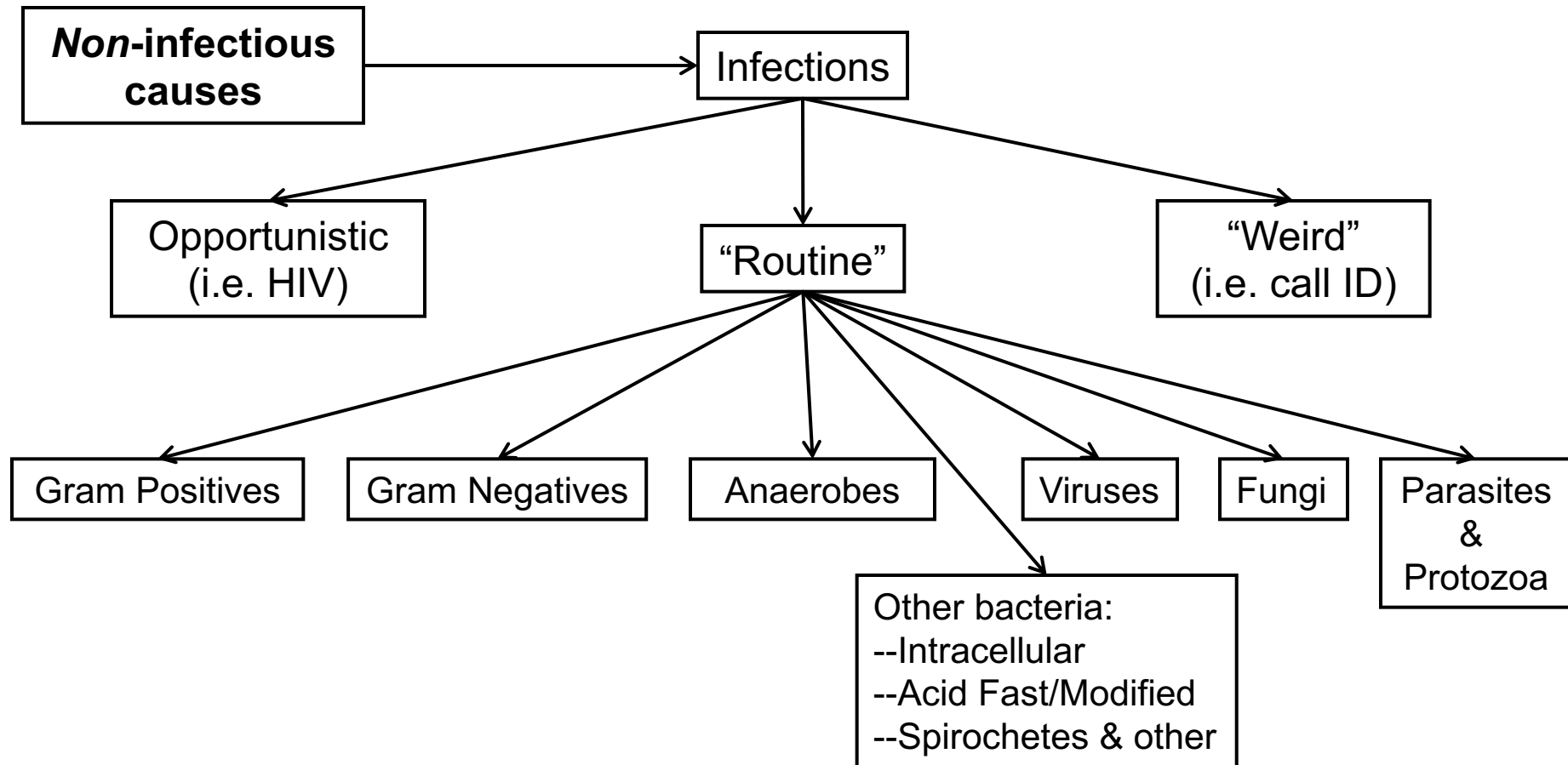
- “Presence or absence of normal brain function”
- “mental status” changes (MSΔ)
- Personality changes
- Focal neurologic deficits
- Speech dysfunction
- Problem is sometimes it’s hard to distinguish...
- ...*and* there can be “meningoencephalitis” (e.g. *Listeria monocytogenes*), so...
- Always have low threshold to include encephalitis in differential

Case presentation

- 12 yo F
- Severe HA, stiff neck
- Temp 39.5
- Able to answer questions initially
- No bites, trauma
- Differential?



An ID doctor's way of considering ID Cases

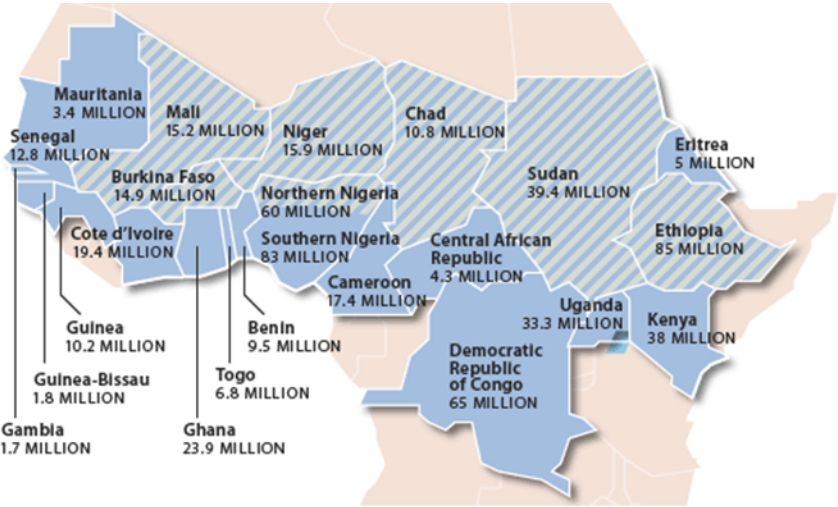
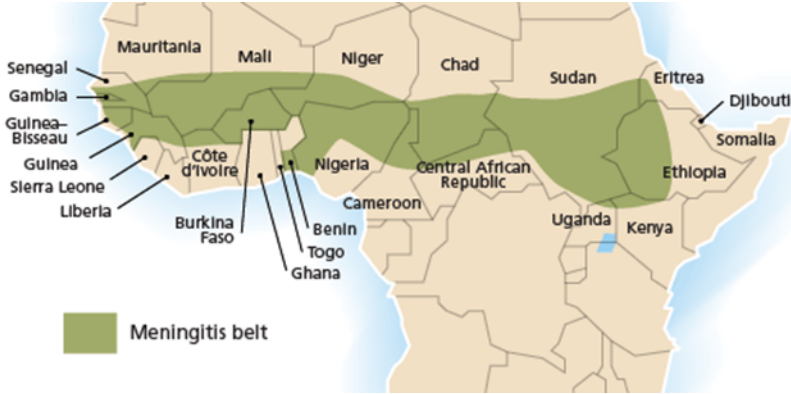


Remember: organize your differential

- **Noninfectious:** unlikely—leukemia or lymphoma? SLE?
- Infectious:
- “Standard” bacterial—high likelihood
- Miscellaneous bacterial—*Rickettsia* infxn? Leptospirosis?
- Viral—HSV encephalitis? Why less likely? Other viruses?
- Fungal—Aspergillus? Candida? Crypto? Histo? Why less likely?
- Parasitic—Malaria? Trypanosoma brucei? Why less likely?
- HIV OIs? What are the major CNS infections in advanced HIV?

Bacterial meningitis

- Major causes:
- *Strep pneumoniae*
- *Neisseria meningitidis*
- *E. coli* (newborns... and adults?)
- *Haemophilus influenzae* (decreasing with vaccine)
- and...
- *Listeria monocytogenes* (clinically slightly different)



Meningitis etiology by age, risk factor (US)

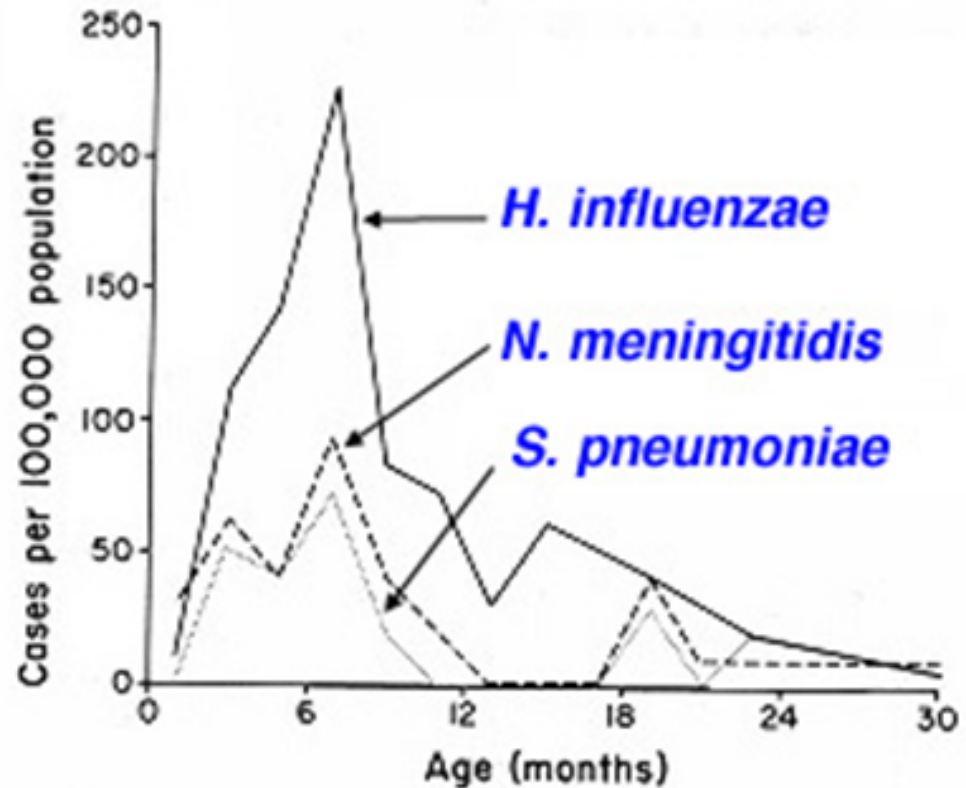
Table 1. Common Bacterial Pathogens

Age/Predisposing Factor	Pathogens
<1 mo	GBS, <i>E coli</i> , <i>L monocytogenes</i>
1-3 mo	GBS, <i>E coli</i> , <i>L monocytogenes</i> , <i>S pneumoniae</i> , <i>N meningitidis</i> , Hib
>3 mo	<i>S pneumoniae</i> , <i>N meningitidis</i>
>50 y	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , gram-negative bacilli
Immunocompromised state	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , gram-negative bacilli (including <i>P aeruginosa</i>)
Post neurosurgical procedure, head trauma	<i>S aureus</i> , coagulase-negative staphylococci, gram-negative bacilli (including <i>P aeruginosa</i>)
CSF shunt	Coagulase-negative staphylococci (<i>S epidermidis</i>), <i>S aureus</i> , gram-negative bacilli (including <i>P aeruginosa</i>)

CSF: cerebrospinal fluid; E coli: Escherichia coli; GBS: group B streptococcus; Hib: Haemophilus influenzae type b; L monocytogenes: Listeria monocytogenes; N meningitidis: Neisseria meningitidis; P aeruginosa: Pseudomonas aeruginosa; S aureus: Staphylococcus aureus; S epidermidis: Staphylococcus epidermidis; S pneumoniae: Streptococcus pneumoniae.
Source: References 1, 12.

Meningitis in children (US graph, 1985)

- *H. flu* dramatic decreases with introduction of vaccine; now very rare in US
- *Neisseria* likely to be more common in Liberia than US

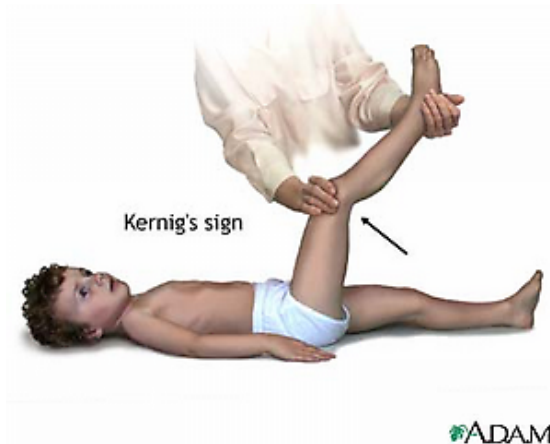


Acute meningitis in children: clinical presentation

- In adults, at least one of the following are seen in nearly all cases: fever, HA/MSΔ, neck stiffness
- The abrupt onset and neck stiffness in this case is what makes bacterial meningitis most likely dx
- In younger children, meningitis can be more difficult to spot, as signs/sx more nonspecific
- Fever *or* hypothermia
- Poor feeding
- Diarrhea
- Vomiting
- Lethargy, irritability
- Seizures
- Older children may have photophobia, focal neurologic signs

Meningitis: physical exam

- Infants: bulging fontanel
- Older children:
- Kernig's Sign
- Brudzinski's Sign
- All signs not very sensitive but more specific (helpful if positive, not if negative)



Reconsideration of Case

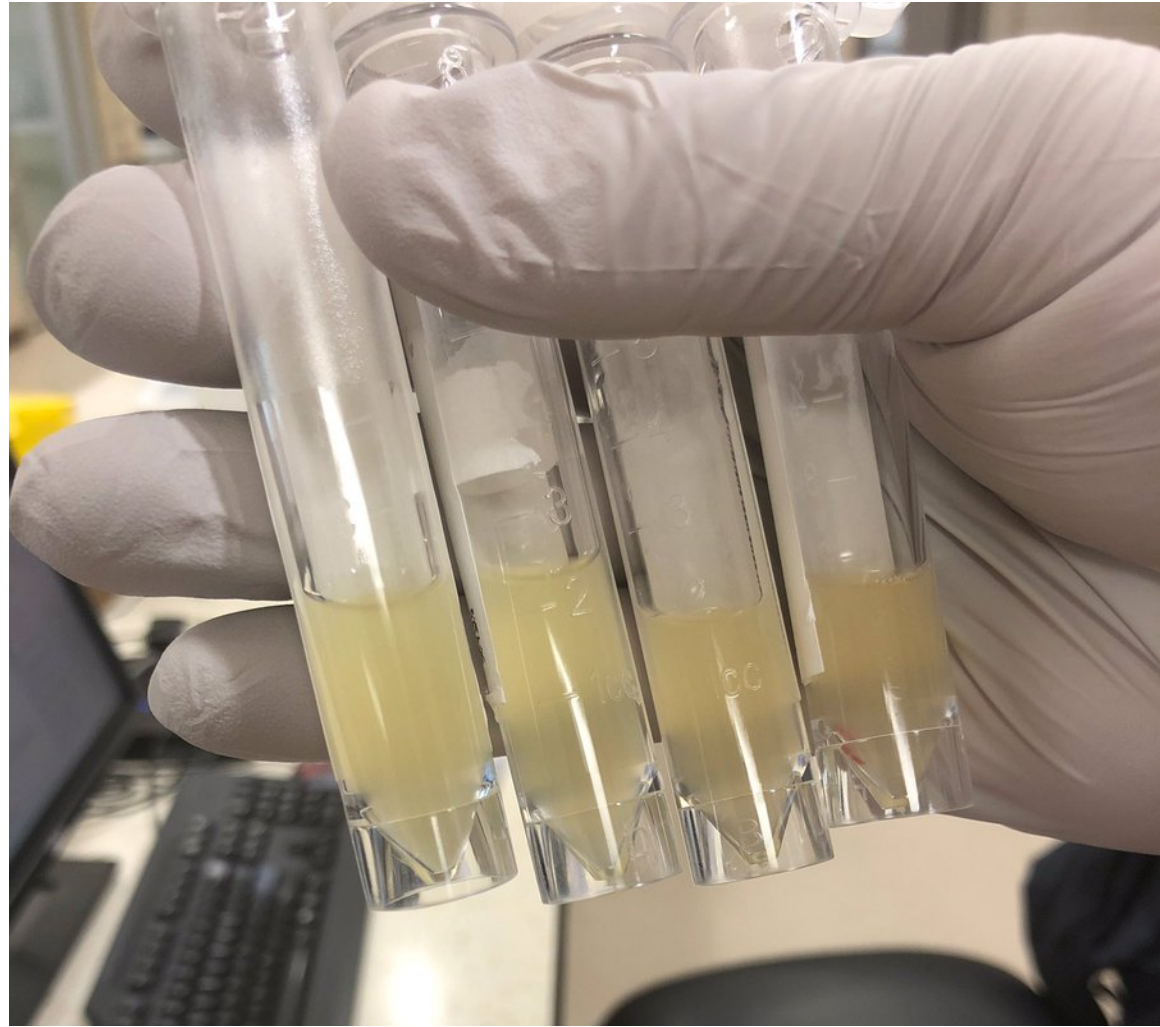
- 12 yo F, HA, stiff neck, Temp 39.5
- Able to answer questions initially, gradually obtunded



What to do next?

- A. Start cloxacillin.
- B. Start chloramphenicol.
- C. Order CXR.
- D. Start griseofulvin.
- E. Perform spinal tap.
- F. Start ceftriaxone 1 gram daily.

- Cloxacillin is best used for staph.
- A chest XR will not help you in further diagnosis.
- Griseofulvin is good for ringworm, not meningitis.
- Meningitis dose Ceftriaxone is 2 grams q12hr, not 1 gram q24.
- Chloramphenicol (IV, PO) will cover relevant organisms—which are...?
- Under ideal conditions, a spinal tap is *critical* in patients with HA, fever +/- MSΔ.



Which of the following is most likely suggestive of Pneumococcal or Meningococcal meningitis?

- A. “turbid,” WBC 2000 (90% PMN), prot 300, glu 16
- B. “clear,” WBC 5, RBC 250, prot 45, glu 60
- C. “cloudy,” WBC 250 (40% PMN / 60% lymphocyte), prot 300, glu 30
- D. “cloudy,” WBC 150 (80% Eo), prot 100, glu 60
- E. “cloudy,” WBC 100 (“atypical cells”), prot 100, glu 60

Gram-negative meningitis

- Clinically identical to pneumococcal & Neisseria meningitis
- *E coli* most common Gram negative
- Seen most often in neonates
- Can also be seen in elderly or immunosuppressed

- In adults, *E coli* meningitis should prompt what additional measure?
- Give ivermectin—gram-negative meningitis can be due to strongyloides moving through gut wall, causing transient bacteremia & seeding of CNS.

Case #2: 16 yo F

- HA x 3 weeks
- Some intermittent fevers, wt loss
- Unremarkable vitals, physical exam
- CSF: yellow, viscous, WBC 500 (90% L), Prot 300 mg/dL (3 g/L), Glu 22

While you wait for culture results, what action(s) would be reasonable to take?

- A. Give chloramphenicol.
- B. Start rifampin, isoniazid, pyrazinamide, ethambutol, methylprednisolone, and Vitamin B6.
- C. Consider psychiatric issue; headaches don't last that long, she's making it up.
- D. Send HIV serology ("spot").
- E. Place PPD.

Tuberculous meningitis (TBM)

- Exact incidence hard to know
- May account for ~5% of extrapulmonary TB
- Can have acute or indolent course (several weeks to 9 months)
- Diagnosis difficult; often made clinically
- PPD *not* useful in dx
- Classic TBM tap: ↑WBC, mostly lymphs, ↑prot, ↓glu (bacteria's food is glucose!)
- Tx with anti-TB meds plus steroids initially
- HIV testing in pts with suspected TBM.

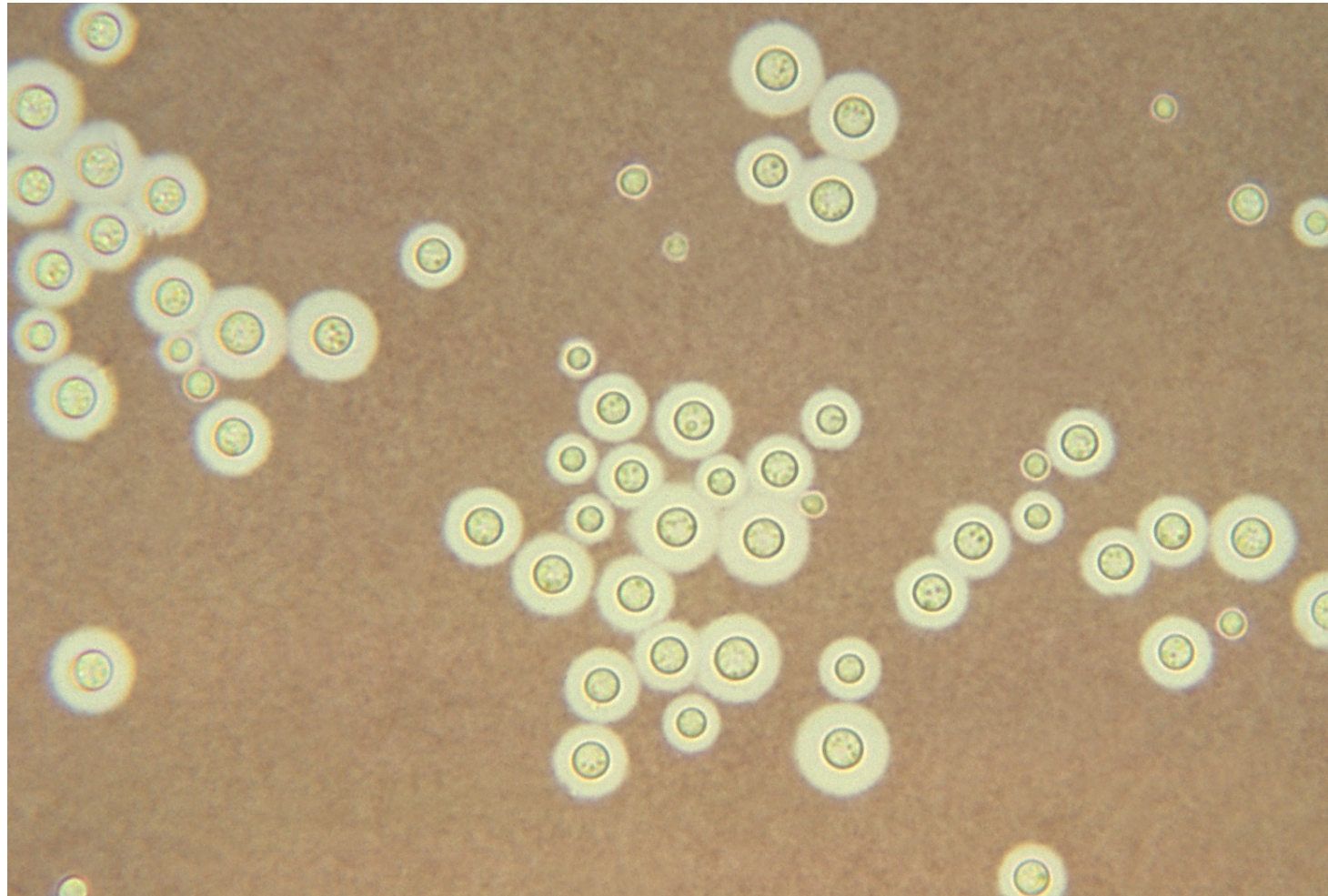
What would be the major differences in the spinal tap of a patient with TBM and a patient with fungal meningitis?

- A. TBM usually has low glucose; fungal meningitis rarely does.
- B. TBM usually has high protein; fungal meningitis has normal protein.
- C. TBM usually has lymphocytes and high WBC; fungal meningitis has high WBC but with neutrophils.
- D. There are no major differences.

Fungal meningitis

- Major concern is *Cryptococcus neoformans*
- Also Candida, aspergillus (rare)
- Crypto dx: India Ink, serum/CSF Crypto Ag
- ~10% of pts in sub-Saharan Africa with CD4 <100 are + for Crypto Ag & should be on prophylactic Fluconazole
- Major problem in IRIS in Africa—heavy cause of mortality in pts beginning ARVs
- Ampho B drug of choice; fluconazole

India Ink in CSF



9 yo M

- HA 3 days, fever
- Temp 38. 2 in exam room
- + Meningismus; Kernig's & Brudzinski's negative
- CSF: 32 WBC, 100% lymph, glu 63, prot 50, clear fluid

What do you want to do?

- A. Start fluconazole.
- B. Observe; provide IVF.
- C. Order Toxoplasmosis IgM serology.
- D. Start ceftriaxone 2 grams IV q12hr.
- E. Begin cimetidine.

Viral meningitis, aka “Aseptic meningitis”

- Many potential causes
- Major players are enteroviruses & herpesviruses (HSV2>VZV>CMV>HSV1>HHV6)
- CSF low WBC, lymph>>neutrophil, protein normal or slightly elevated, glu normal
- Supportive treatment
- Adults: recurrent meningitis caused by HSV2 aka “Mollaret’s meningitis”

CSF analysis: know your CSF

	Normal	Bacterial	Viral	Fungal/TB
Pressure (cmH2O)	5-20	> 30	Normal or mildly increased	
Appearance	Normal	Turbid	Clear	Fibrin web
Protein (g/L)	0.18-0.45	> 1	< 1	0.1-0.5
Glucose (mmol/L)	2.5-3.5	<2.2	Normal	1.6-2.5
Gram stain	Normal	60-90% Positive	Normal	
Glucose - CSF:Serum Ratio	0.6	< 0.4	> 0.6	< 0.4
WCC	< 3	> 500	< 1000	100-500
Other		90% PMN	Monocytes 10% have >90% PMN 30% have >50% PMN	Monocytes

56 yo F with lethargy x72 hours

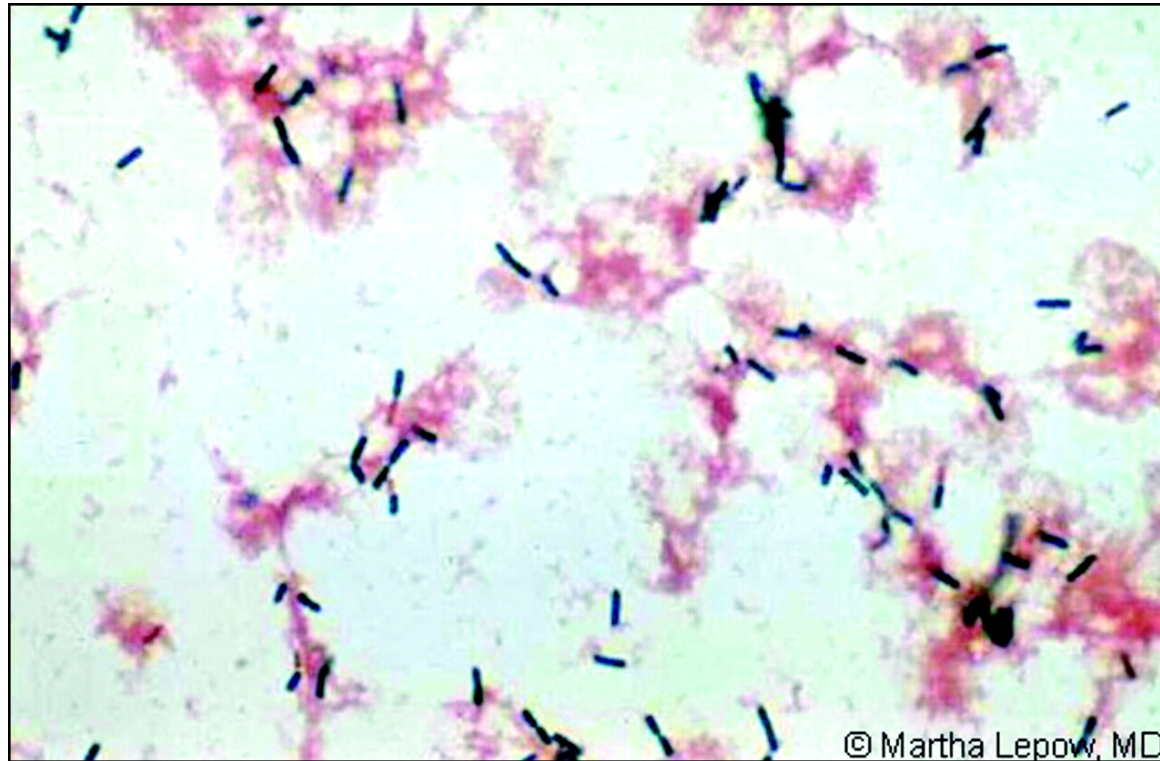
- Intermittent fevers
- Speech difficulties—looks like stroke
- No gross motor deficits
- Temp on exam 38.0, vitals otherwise stable
- No meningismus

What do you want to do next?

- Obtain CXR.
- Start atenolol for hypertensive CVA.
- Test for HIV.
- Obtain CSF.
- Send sputum for AFB.

CSF

- WBC 120 (50 N, 50 L)
- Glu 28
- Prot 60
- Gram Stain:



What do you want to do now?

- Start ARVs (for HIV).
- Increase atenolol for CVA.
- Start IV ampicillin.
- Start 4-drug TB treatment.
- Start Flagyl.

Listeria

- “Meningoencephalitis” —can present either as meningitis, or encephalitis, or both
- Likes to live on meats & cheeses left out in warm weather
- Gradual or abrupt onset
- Very young or old (>60); also in HIV!
- Often with CVA-like sx in adults
- High mortality if not treated
- Tx: ampicillin

Referred to ER from clinic

- 35 yo M with focal neurologic deficits
- Sx worsened 4-6 wks; brought in by family
- R sided weakness lower extremity
- Confusion
- Vitals: 36.6, 100, 106/60, RR 22, 98%
- Exam: cachexia, heart/lungs/abdomen all normal; difficulty standing, cannot walk without assistance

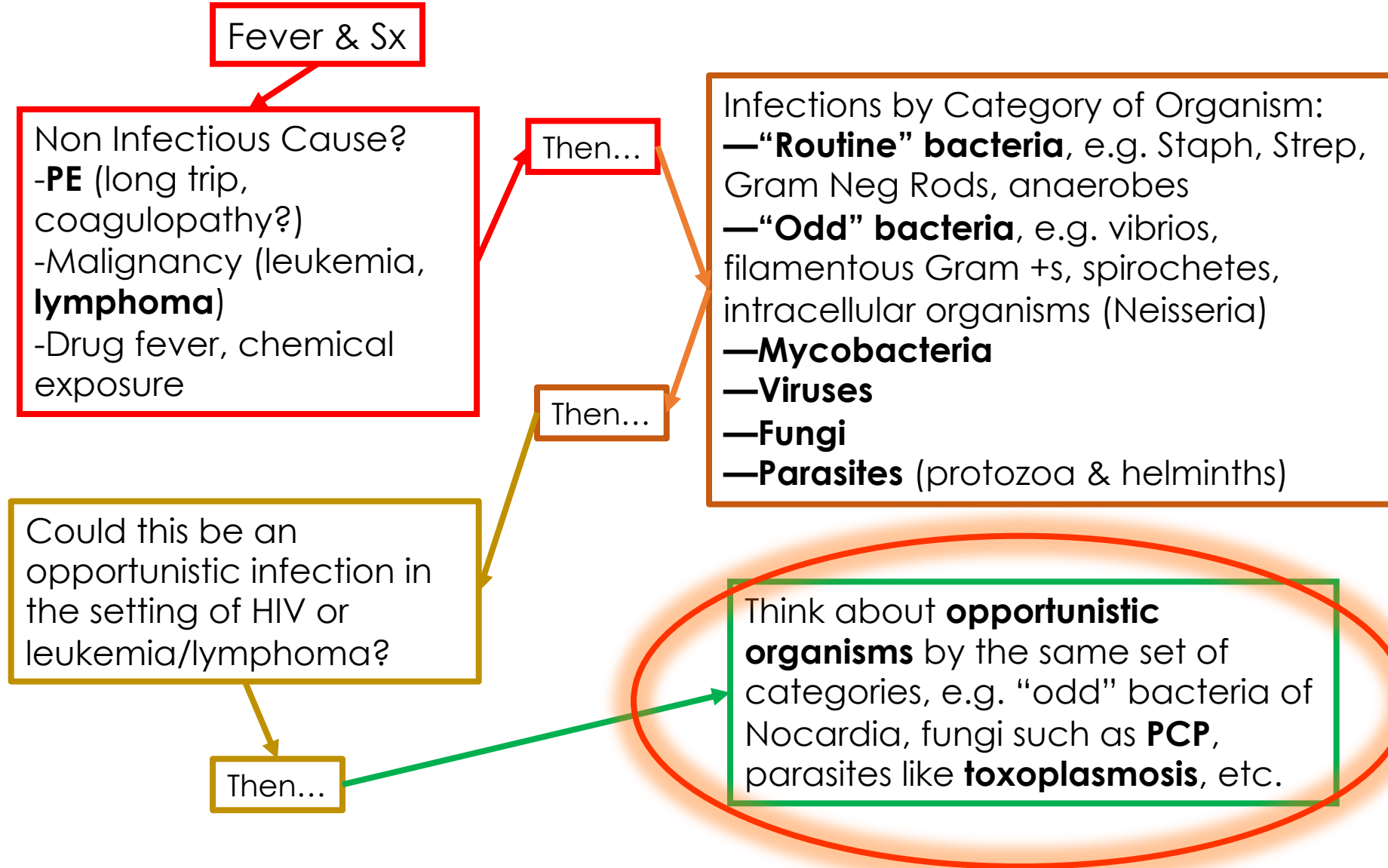
Which of the following statements are true?

- A. A careful evaluation of this patient's oral cavity may give clues to the diagnosis.
- B. The rapid administration of ampicillin and gentamicin is likely to help.
- C. This patient probably has a CVA.
- D. A chest x-ray should be ordered.
- E. The most likely diagnosis is TB meningitis.

The patient has thrush. Which of the following organisms are likely causes of this presentation?

- A. *Strongyloides stercoralis*.
- B. *Toxoplasma gondii*.
- C. *Actinomyces israelii*.
- D. *Cryptococcus neoformans*.
- E. Rift Valley Fever.
- F. A complication of EBV infection.
- G. JK Virus.
- H. PCP

An ID doctor's approach to DDx in febrile illness



CNS infections in HIV

- HIV can have subtle presentations, but thrush is essentially diagnostic
- Always suspect HIV in pts with wasting or cachexia or recurrent illness
- If you diagnose HIV in setting of *one* illness (e.g. CNS disease), remember that HIV patients can *also* have *other* diseases as well—this patient had RR of 22, which is tachypnea! Consider lung infections like PCP or TB!

CNS infections in HIV con't: most common OIs

- CD4 <250: CNS lymphoma 2ndary to EBV
- CD4 <200: cryptococcosis
- CD4 <100: toxoplasmosis
- CD4 <50: Progressive Multifocal Leukoencephalopathy (PML) due to JK virus

Diagnosis

- CNS lymphoma: CT scan
- Cryptococcosis: India Ink prep of CSF; also spinal tap typically very high pressure, fluid “shoots out”
- Toxoplasmosis: serology
- PML dx requires MRI

Treatment

- CNS lymphoma: none, ARVs may help
- Crypto: amphotericin B or fluconazole, serial spinal taps in patients with ongoing HA or blurry vision (to ↓ intracranial pressure)
- Toxo: pyrimethamine/sulfa
- PML: ARVs, no specific treatment (anywhere)

Dog bite

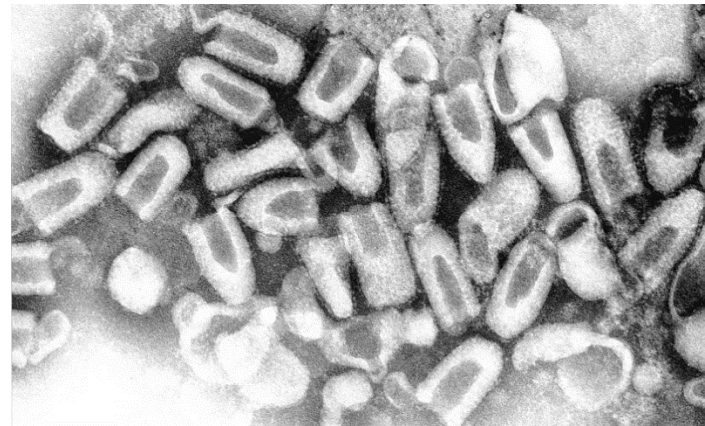
- 15 yo M bitten by dog yesterday
- Dog ran away
- Hand is red, swollen, tender; elbow tender as well
- Remainder of exam is normal

Further treatment includes?

- A. IV ampicillin and gentamicin.
- B. This patient does not have rabies & can be sent home.
- C. This patient does have rabies, nothing can be done, send him home.
- D. Start rabies PEP (rabies vaccine).
- E. PO fluconazole for *Candida canimorsus*, a known fungal pathogen from dogs.

Rabies virus

- In Rhabdovirus family (Lyssavirus)—nonsegmented negative-sense RNA virus in bullet-shaped envelope
- ~30,000 – 70,000 deaths each year (still!)
- Retrograde passage through peripheral nerves to CNS
- Mainly affects brainstem



Rabies: clinical

- Incubation usu ~1-3 months
- Prodrome: nonspecific; paresthesias @ bite site
- Encephalitic or “Furious” rabies (~80%):
hydrophobia/aerophobia, pharyngeal spasms,
hyperactivity, aggression
- Flaccid or “Dumb” rabies (~20%): quadriparesis—
similar to GBS
- Death in ~2-3 wks from prodrome; almost universally
fatal (one known survivor—Jeanna Giese pictured
previously)
- Clinical dx

Post-Exposure Prophylaxis (PEP) in USA

- Two interventions:
 - Rabies vaccine (IM only—not intradermal)
 - Rabies Immune Globulin (HRIG)—given locally at wound site and distantly IM
- 5 doses: day 0, 3, 7, 14, 28 in deltoid

50 yo M

- Presents with SZR, FVR, confusion
- 3 days PTA has FVR/HA/confusion
- 1 day PTA had SZR, lost consciousness 10-15 mins

Exam

- 37.8, 110/90, 66, 18 with 90% RA sats
- Neck supple, no lymphadenopathy
- Lungs clear
- III/VI SEM with radiation to carotids
- Abd benign, no LE edema, no rash
- Neuro: normal except for confusion

Data

- Lytes: 132 / 3.5 / 102 / 26
- WBC: 14.2 (82 N, 6 Bands, 10 L, 1 Atypical lymph, 1 M)
- Hct: 47
- Plt: 267
- CXR: bibasilar atelectasis

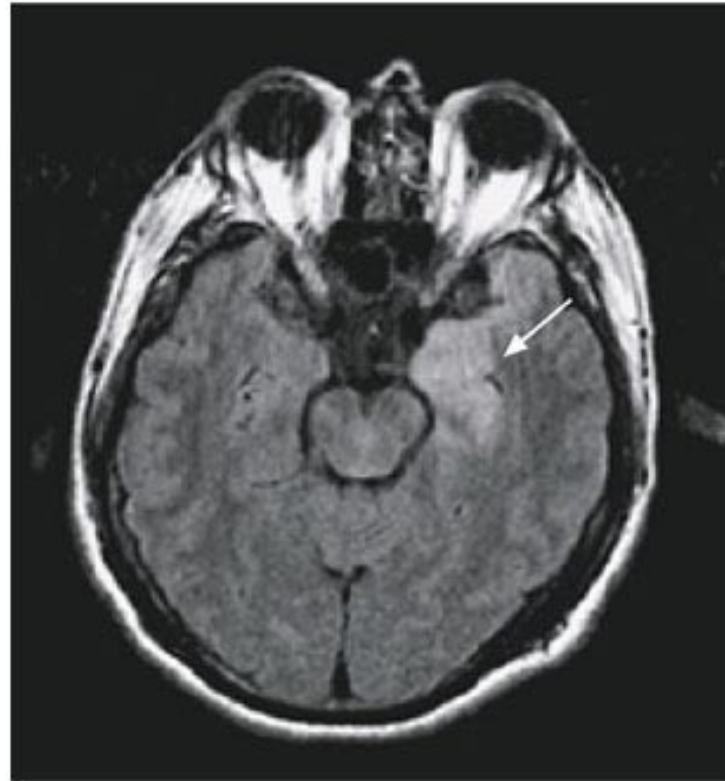
What do you want to do next?

- A. Send for psych +/- neuro consult for acute psychosis.
- B. Begin haldol; you do not require psych consult to treat this syndrome.
- C. Obtain lumbar puncture.
- D. Begin IV amphotericin B.

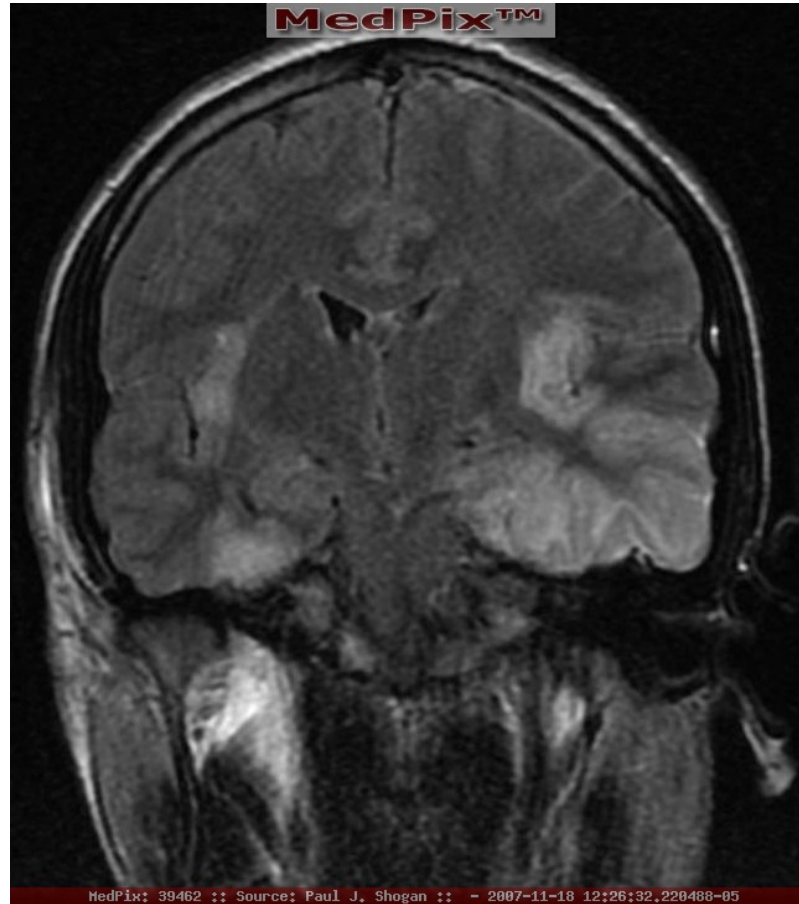
Tap

- CSF clear
- 9 RBC
- 138 WBC (44 N, 23 L, 33 M)
- Glu 83
- Prot 45
- Gram stain: monos & neuts, no organisms

MRI FLAIR (axial)



MRI FLAIR (coronal)



Diagnosis?

Herpes Simplex Encephalitis (HSE)

- Almost exclusively HSV-1
- Acute inflammation, congestion and/or hemorrhage of brain *predominantly in temporal lobes*
- Can be primary or recurrent (primary in ~33% of cases, most of those <18 yo)
- Pathogenesis not perfectly understood

HSV con't

- Most common cause of sporadic viral encephalitis in world
- 1 per 300,000 individuals
- ~10-20% of all viral encephalitides
- *Throughout the year, pts of all ages*
- In US, Caucasians>African Americans

Clinical presentation

- Usu acute (<1 wk)
- FVR +/- (any of) MS Δ , \downarrow LOC, dysphasia/aphasia, focal CN deficits, SZR seen in ~90% of pts
- Can also see specific syndromes:
 - Hypomania
 - Klüver-Bucy syndrome
 - Amnesia

DNA restriction-enzyme analysis of HSV isolates obtained from patients with encephalitis. Whitley R, NEJM 307 (1982), 307; 1060-62.

Table 1

Comparison of findings in "brain-positive" and "brain-negative" patients with herpes simplex encephalitis (Whitley et al., 1982a,b)

	Number (%) of patients	
	Brain-positive (n = 113) ^a	Brain negative (n = 85) ^a
Historical findings		
Alteration of consciousness	109/112 (97)	82/84 (98)
CSF pleocytosis	107/110 (97)	71/82 (87)
Fever	101/112 (90)	68/85 (78)
Headache	89/110 (81)	56/73 (77)
Personality change	62/87 (71)	44/65 (68)
Seizures	73/109 (67)	48/81 (59)
Vomiting	51/111 (46)	38/82 (46)
Hemiparesis	33/100 (33)	19/72 (26)
Memory loss	14/59 (24)	9/47 (19)
Clinical findings at presentation		
Fever	101/110 (92)	84/79 (81)
Personality change	69/81 (85)	43/58 (74)
Dysphasia	58/76 (76)	36/54 (67)
Autonomic dysfunction	53/88 (60)	40/71 (56)
Ataxia	22/55 (40)	18/45 (40)
Hemiparesis	41/107 (38)	24/81 (30)
Seizures	43/112 (38)	40/85 (47)
Focal	28	13
Generalized	10	14
Both	5	13
Cranial nerve defects	34/105 (32)	27/81 (33)
Visual field loss	8/58 (14)	4/33 (12)
Papilledema	16/111 (14)	9/84 (11)

^a Of 202 patients assessed.

HSE: Dx

- Avg CSF WBC ~100; protein ~100
- CSF RBC is *not* diagnostic for HSE (and likewise *lack* of CSF RBC doesn't rule it out)
- (MRI with temporal lobe enhancement in appropriate clinical picture is highly suggestive)
- In resource-abundant settings HSV PCR (~94% sens, ~98% specific) is primary means of diagnosis

Tx and Prognosis

- IV acyclovir 10 mg/kg q8hr, dose adjust for renal insufficiency; if no IV, give po (limited data supporting use)
- Total duration 14-21 days
- Mortality: untreated 70%
- Mortality with treatment ~20%, *but...*
- About half of pts with some moderate to serious neurologic deficit