Brain Infections: Terms, Syndromes, Bugs & Drugs

Cheryl A. Jay, MD
Clinical Professor
UCSF Department of Neurology
SFGH Neurology Service

Brain Infections

Terms
Cases: syndromes, bugs & drugs
- meningitis
  - bacterial
  - aseptic (often, but not always, viral)
  - chronic meningitis/meningoencephalitis
- encephalitis
  - seasonal
  - year-round

CNS Infections: Terms

(lepto)meningitis
encephalitis
myelitis
neologisms:
  - meningoencephalitis
  - encephalomyelitis
  - etc.

inflammation ≠ infection
Case 1: ED Visits for Headache

Middle-aged man comes to the ED for headache x several days; stiff neck & diplopia x 24 hours
- glucose intolerance, not on hypoglycemic agents
- seen 2 days previously and sent home on HCTZ & ibuprofen after head CT negative

PE: T 38.1, BP 193/103, P 121, RR 30, 6/10 head pain
- looks ill, stiff neck, no rash
- alert, fully oriented & conversant
- mild R papilledema, unreactive R pupil, R eye nearly immobile, decreased abduction L eye (R CN 3 & CN 6 palsies + L CN 6 palsy)
- normal reflexes, strength, sensation; too sick to walk

My working diagnosis is...

1) Bacterial meningitis
2) Meningoencephalitis
3) Aseptic meningitis
4) Viral encephalitis

This patient needs a CT before LP...

1) yes
2) no
**Bacterial Meningitis: Key Points**

**Classic triad:** fever, stiff neck, AMS
- Add headache & 95% of patients have 2 or more features (all have at least one).
- More on meningismus:
  - May not be prominent in the young & the elderly.
  - Brudzinski’s & Kernig’s signs: specific, but not sensitive.

**Setting matters:**
- Community-acquired
- Nosocomial (usually post-traumatic, including neurosurgical)

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**Bacterial Meningitis: CT Before LP in Adults**

**Immunocompromised:** HIV, transplant recipients & others on immunosuppressants

**History of cerebral disease:** mass lesion, stroke, focal infection

**New-onset seizure:** within a week

**Papilledema:** rare presenting manifestation

**Abnormal level of consciousness**

**Focal neurologic deficit:** inability to answer 2 questions or follow 2 commands, aphasia, gaze palsy, visual field deficit, facial palsy, arm or leg drift


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**Before ordering the CT, I would…**

1) get blood cultures
2) give dexamethasone 10mg
3) give vancomycin + ceftriaxone 2g
4) 1 & 3
5) 1, 2 & 3
Management algorithm for adults with suspected bacterial meningitis.

Suspected for bacterial meningitis
- Yes

- Intoxication, history of CNS illness, new onset seizures, psychosocial, altered consciousness, or focal neurological deficits?
- Yes
- No

- Blood cultures and lumbar puncture STAT
- Dexamethasone* + empirical antimicrobial therapy
- Yes
- No

- CSF findings + bacterial meningitis
- Yes
- No

- Positive CSF Gram stain
- Yes
- No

- Dexamethasone* = empirical antimicrobial therapy
- Dexamethasone* = targeted antimicrobial therapy

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Case 1: Initial Treatment, Events & Results

Rx: dexamethasone 10mg + ceftriaxone + vancomycin + ampicillin

While waiting for CT, acute unresponsiveness & hypoxemia: intubated, paralyzed, sedated.

Labs: wbc 23K
- Na+ 131, K+ 3.3, creatinine 0.75, glucose 272 plt 278, INR 1.2
- rapid HIV negative
- CXR: ? left basilar infiltrate
- blood cultures sent

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Case 1: A Working Diagnosis

CSF: OP 28cm, cloudy
- protein 415, glucose 41 (serum 272)
- 2230 rbc, 13,700 wbc (86% polys)
- gram stain negative
dx: community-acquired bacterial meningitis (? pneumococcal)

ICP monitor & 3% saline, pressors
Bacterial Meningitis: CSF

**During the LP:** cloudy, OP >200mm  
**Routine studies:**  
- wbc (*polys*): 1000 - 5000/mm³  
- protein: >200 mg/dL  
- glucose: CSF/serum <0.4  
*Gram stain: positive >60% of pts (97% specific)  
*culture (blood may be + when CSF not)  
*a affected by prior antibiotic treatment  
**Other studies:**  
- latex agglutination: can identify pathogen, but not exclude meningitis, in treated pts  
- PCR: stay tuned

Bacterial Meningitis: Microbial Trends & Treatment

**Good news:** sharp drop in *H flu* meningitis  
**Bad news:** more resistant pneumococcus  
**Empirically, for adults:** vancomycin + 3rd generation cephalosporin &…  
- add ampicillin if Listeria is a concern (> age 50, renal disease, alcoholism, diabetes, other immunocompromised states, as well as infants)  
- use cefipime or ceftazidime or meropenem if Pseudomonas is a concern (nosocomial)

Recommendations for empirical antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition (A-III).

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Common bacterial pathogens</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td><em>Streptococcus agalactiae</em>, <em>E. coli</em>, <em>L. monocytogenes</em>, <em>Klebsiella</em></td>
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<tr>
<td>1-12 months</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>E. coli</em>, <em>Klebsiella</em>, <em>S. epidermidis</em></td>
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<tr>
<td>&gt;1 year</td>
<td><em>H. influenzae</em>, <em>S. pneumoniae</em>, <em>E. coli</em>, <em>Klebsiella</em>, <em>S. epidermidis</em>, <em>Listeria</em></td>
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<tr>
<td>Bloodstream route</td>
<td><em>Staphylococcus aureus</em>, <em>Pseudomonas aeruginosa</em>, <em>Acinetobacter baumannii</em></td>
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<tr>
<td>Penetrating wounds</td>
<td><em>Klebsiella</em>, <em>A. baumannii</em>, <em>S. aureus</em>, <em>P. aeruginosa</em>, <em>E. coli</em>, <em>S. epidermidis</em>, <em>Fusobacterium</em>, <em>Bacteroides</em></td>
<td></td>
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<tr>
<td>CF clinic</td>
<td><em>P. aeruginosa</em>, <em>S. aureus</em>, <em>Klebsiella</em>, <em>A. baumannii</em>, <em>C. neoformans</em>, <em>Cryptococcus</em></td>
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</table>

Recommendations for antimicrobial therapy in adult patients with presumptive pathogen identification by positive Gram stain.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Recommended therapy</th>
<th>Alternative therapies</th>
</tr>
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<tbody>
<tr>
<td>Staphylococcus pneumonia</td>
<td>Vancomycin or quinolone</td>
<td>Meropenem (GCS) Flucloxacillin + B-R</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Third-generation cephalosporin</td>
<td>Penicillins (p, quinolone, clindamycin, fluoroquinolone), azithromycin</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Ampicillin + piperacillin</td>
<td>Tetracyclines, sulphonamides (SE)</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>Amoxicillin + piperacillin</td>
<td>Tetracyclines, sulphonamides (SE)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Third-generation cephalosporin</td>
<td>Ceftriaxone (GCS) Flucloxacillin + B-R</td>
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</table>

**Note:** All recommendations are A/B, unless otherwise noted. In children, ampicillin is added to the standard therapeutic regime of amoxicillin or ceftriaxone also as standard single. L. monocytogenes is considered and in an ampicillin-resistant strain is also effective in meningitis.
- Ceftriaxone or cefotaxime
- Some agents would add rifampicin if meningococcal is also given (B-R)
- Gatifloxin or moxifloxin
- Addition of an anti-meningococcal should be considered.


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**DECAYTHASONE IN ADULTS WITH BACTERIAL Meningitis**

Joie A. Grant, MD, and Dorothy K. Wolf, MD. For the Survivors DecaMethylene Adjuvant in Bacterial Meningitis Study Investigators

**Glasgow Outcome Score of 5 (back at work or school) versus 1 (dead) to 4 (independent ADL): risk reduction 0.59 (0.37-0.94, p<0.03)**

**Mortality:** risk reduction 0.48 (0.24-0.96, p<0.04)

**No difference in GI bleeding between treatment & control groups**

**Clearest benefit in pneumococcal meningitis**

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**Bacterial Meningitis & Dexamethasone, Recent Papers**

**Meta-analysis:** Europe + Malawi (adult & pediatric) + Vietnam + South America (2029 participants)

- "The benefit of adjunctive dexamethasone for all or any subgroup of patients with bacterial meningitis thus remains unproven.


**Cochrane:** 24 trials, 4041 participants

- "Data support the use of corticosteroids in patients with bacterial meningitis in high-income countries. We found no beneficial effect in low-income countries."


**Pneumococcal meningitis, Netherlands**

- dexamethasone: 3% 1998 – 2002 versus 84% 2006 – 09

- 11% increase in GOS 5, 10% fall in mortality


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Ucsfphhui
Bacterial Meningitis: Complications & Outcome

Anticipate complications:
- acute, severe illness: sepsis, GI bleed, DVT, decubiti, malnutrition
- hypo/hypernatremia
- inflammed meninges: hydrocephalus, cerebral edema, stroke, cranial neuropathies (including hearing loss)

US case fatality rates ~20%: beware pneumococcal & gram negative meningitis

Case 1: Unexpected Culture Result & a Difficult Course

CSF & blood cultures: MRSA

Persistent AMS, cranial neuropathies, with quadriparesis

At discharge to SNF 3 months later: trach, PEG, following simple commands, right CN3 palsy, immobile left eye, quadriparetic

Aseptic Meningitis

Self-limited meningeal inflammatory syndrome, usually viral
- enterovirus: classic summer outbreaks
- HSV-2: may be recurrent
- HIV: as part of seroconversion & a whole host of others

Uncomfortable, but neurologically normal, pt:
- mild lymphocytic pleocytosis & protein elevation, normal glucose

Parenchymal dysfunction = alternative dx
- noninfectious causes: autoimmune, drugs (IT agents, oral TMP/SMX, NSAIDs, IV Ig, OKT3 & others), leaking cystic brain tumors, missed SAH
- infections: early or partially treated acute bacterial meningitis, neurosyphilis, early TB or other chronic meningitides
Chronic Meningitis/Meningoencephalitis

Meningeal inflammatory syndrome, with lymphocytic pleocytosis, for 30 days or more
Pts often come to attention sooner: new, persistent headache; AMS or other parenchymal dysfunction
Consider: aseptic meningitis “plus” or culture-negative bacterial meningitis, especially when not responding to empiric antibiotics

Enormous differential: “common” causes
- infectious: spirochetes (syphilis, Lyme), TB, fungi (crypto, coci, histo), parasites
- noninfectious: sarcoid, vasculitis (systemic or primary CNS), neoplastic, uveomeningitic syndromes

Chronic Meningitis: Less Common Causes

Infectious
- atypical bacteria: anaerobes, brucella, nocardia, listeria, actinomycyes
- fungi: candida, blasto, among others
- viruses: HIV, chronic enterovirus (hypogam); rarely mumps & LCM
- parasites: Taenia solium, amoebas

Parainfectious:
- partially treated bacterial meningitis
- parameningeal infection
- SBE or bacteremia

Noninfectious
- medications
- collagen vascular disorders
- missed SAH

Case 2: Febrile, vomiting, agitated, disoriented

Elderly Central American man with DM, htn, hyperlipidemia, hyperparathyroidism, BPH brought in for above symptoms for several hours, with headache the day prior.

PE: T 38.5, BP 170/80, P 115
- agitated, moaning, no meningismus
- disoriented, post-surgical pupils, MAE, absent ankle reflexes, toes down

Initial studies:
- wbc 10.4, Hct 38.9, plt 280, Na+ 137, creatinine 0.91,
- glucose 206, normal calcium & LFT's
- normal CXR, U/A: blood cultures sent unsuccessful LP attempt in ED
Assuming no drug allergies, I would treat with...

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<tr>
<td>1)</td>
<td>vancomycin + ceftriaxone</td>
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<td>2)</td>
<td>vancomycin + ceftriaxone + ampicillin</td>
</tr>
<tr>
<td>3)</td>
<td>dexamethasone + vancomycin + ceftriaxone</td>
</tr>
<tr>
<td>4)</td>
<td>dexamethasone + vancomycin + ceftriaxone + ampicillin</td>
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</table>

I would also treat with IV acyclovir...

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<tbody>
<tr>
<td>1)</td>
<td>yes</td>
</tr>
<tr>
<td>2)</td>
<td>no</td>
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Case 2: Fever & AMS in an Elderly Man (& No CSF)
Encephalitis: Key Points

Cause identified in up to 70%
- Infectious: often, but not always, viral
- Post-infectious/vaccination: acute disseminated encephalomyelitis
- Noninfectious (10%): paraneoplastic + chronic meningitis differential above

Important clues for infectious encephalitis:
- Exposure history: season, travel, occupation, pets, ill contacts
- Systemic involvement: eyes, skin, lung, liver, kidneys

Treat empirically (and work up for) HSV encephalitis, while considering other etiologies.

Encephalitis: Many Causes, Fewer Treatments

California Encephalitis
- Project, 1998-2010: 626 pts
- Enterovirus (155)
- HSV-1 (80)
- West Nile (65)
- VZV (60)
- EBV (42)
- TB (31)
- Bartonella spp (16)
- Balamuthia mandrillaris (13)
- Influenza (13)


Selected therapies:
- HSV: acyclovir (A-I)
- VZV: acyclovir (B-III)
- CMV: gancyclovir + foscarnet (B-III)
- HHV-6: ganclovir or foscarnet (B-III) in immunosuppressed patients
- Influenza: oseltamivir (C-III)
- Measles: ribavirin (C-III)
- HIV: HAART (A-II)


Case 2: CSF, at Last

HD #1: clear CSF, OP not measured
- Protein 72, glucose 69
- 20 rbc, 306 wbc (92% lymphs)
- Gram stain negative

Dexamethasone stopped.

Sitting up, eating lunch, talking with his family by the next morning.
I would…

1) Stop all antibiotics.
2) Stop all antibacterials & continue acyclovir.
3) Stop vancomycin + ceftriaxone.
4) Continue everything, pending cultures.

Case 2: A Gratifying Outcome

- CSF HSV-1 PCR positive
- 10 days of IV acyclovir
- Doing well post-discharge

Year-Round Encephalitis: Herpes Simplex Virus-1

- ~10% of encephalitis
- Fever, headache, AMS
- most cases from reactivation of latent HSV-1 in olfactory or trigeminal nerves
- unilateral or bilateral frontal or temporal lobe involvement

**Diagnosis:**
- MRI better than CT
- CSF HSV-1 PCR sensitive, specific (false negatives early & >1 week)
- EEG

**High-dose IV acyclovir:**
- 19% mortality (70% in untreated historical controls)
- Only 38% cognitively normal
Seasonal Encephalitis: West Nile

1st described in West Nile district of Uganda, 1937
1999: NYC outbreak
rapid spread across North America
now most common arboviral encephalitis in US

Virology
arthropod-borne virus: summer & fall in temperate regions
flavivirus related to dengue, Japanese encephalitis
Less commonly: mother-to-child (intrauterine, breast-feeding) or by transfusion or transplantation

West Nile Fever most common form


Case 3: Shingles, Headache & Loss of Consciousness

45 y/o woman with sickle trait & recent right thoracic shingles brought to the ED after passing out at home
* Seen in another ED 4 days earlier with painful right thoracic rash & started on PO acyclovir.
* Returned to that ED the following day with headache & stiff neck; acyclovir was stopped.
* Passed out at home after getting out of bed; ? tonic-clonic leg movements but awoke quickly.

PE:
* T 98.9, BP 138/87, P 69, RR 16
* stiff neck, crusting lesions right T6
* alert, conversant, completely normal neurologic examination

Case 3: Meningitis or Meningo[myelo]encephalitis?

Routine labs: normal
lytes, wbc 5.0

CSF: OP 33.5, clear fluid
* protein 56, glucose 64
* 9 rbc, 187 wbc (96% lymphs)

Rx: IV acyclovir, no anticonvulsants
Case 3: VZV Meningitis

**CSF VZV PCR positive**

**More history:** likely convulsive syncope, not seizure

**Headache & stiff neck resolved after several days of IV acyclovir:** LOC, probable convulsive syncope

**Home after a week of IV therapy**

**Brain Infections**

**Meningitis & encephalitis are often, but not always, infectious.**

**Risk factors for brain infections, such as immunocompromise, can mask classical symptoms, such as headache, meningismus & fever.**

**CSF is the cornerstone of diagnosis:** with neuroimaging & systemic cultures, serology.

**Time is brain:** treat as the workup proceeds