Meningitis & Encephalitis

January 2, 2017 by Josh Farkas

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background: meningitis & encephalitis

Meningitis is inflammation of the subarachnoid space, the fluid bathing the brain. Most common causes are bacterial or viral.
**Encephalitis** is inflammation of the brain tissue itself. Most common causes are viral or autoimmune.

<table>
<thead>
<tr>
<th>Typical features of meningitis vs. encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, leukocytosis</td>
</tr>
<tr>
<td>Meningeal irritation</td>
</tr>
<tr>
<td>- Nuchal rigidity</td>
</tr>
<tr>
<td>Mental status alteration</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
<tr>
<td>Focal neurologic findings, e.g.</td>
</tr>
<tr>
<td>- weakness</td>
</tr>
<tr>
<td>- aphasia</td>
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<tr>
<td>- behavior change</td>
</tr>
</tbody>
</table>

### clinical presentations & approach

- Focal neurologic findings and seizures are more characteristic of encephalitis, whereas meningeal irritation is more suggestive of meningitis.
- Among critically ill patients, meningitis and encephalitis are often indistinguishable. For example, patients are often obtunded and thus unable to participate in a detailed neurologic examination.
- The initial treatment approach should encompass the possibilities that the patient may have either meningitis or encephalitis. Eventually, lumbar puncture and MRI are often needed to sort this out.

### when to suspect CNS infection

1) patients being admitted to ICU from the outpatient world

- Intensivists have a huge advantage with regards to diagnosing meningitis/encephalitis, because the patients that we see are all sick.
- In general, CNS infection should be considered when the following criteria are met:
  - 1) Evidence of infection (e.g. fever/hypothermia, leukocytosis, or left-shift).
  - 2) Evidence of neurologic involvement (e.g. altered mental status, severe headache, nuchal rigidity, photophobia, focal neurologic signs).
  - 3) No well-established diagnosis to account for #1-2.
- When in doubt, it's generally better to err on the side of getting a lumbar puncture (especially among intubated patients who can't be closely observed for deterioration).
2) patients who have been in the hospital for awhile

- Fever and altered mental status are extremely common among patients admitted to the hospital.
- It is uncommon for a patient admitted with an unrelated problem to suddenly develop meningitis while in the hospital.
- In general, a lower index of suspicion is appropriate for patients who have been admitted to the hospital for a few days, unless they have a disease process that could cause meningitis (e.g. bacterial endocarditis, pneumococcal bacteremia, ventricular drain).

**management of stuporous/comatose patient with suspected CNS infection**

The pathway below describes how to manage a patient with significant obtundation and probable/definite CNS infection.

**droplet precaution**

- Indicated until meningococcal meningitis excluded.

**empiric steroid & antibiotic**

- If you’re seriously suspecting meningitis, initiate therapy without delay. A three-drug regimen is generally adequate for this purpose (discussed further below (#antibiotic_selection)).
  1) **Dexamethasone** 10 mg IV (or 60 mg IV methylprednisolone if that’s all you have).\(^1\) Steroid should ideally be given simultaneously/before antibiotics, but it’s still recommended up to four hours after the first dose of antibiotic.\(^2\)
  2) **Ceftriaxone** 2 grams IV (or 2 grams of meropenem if patient has history of anaphylaxis to penicillin or cephalosporin allergy).
  3) **Acyclovir** 10 mg/kg IV
- Additionally, consider doxycycline 100 mg q12hr if rocky mountain spotted fever or tick-borne encephalitis is possible.

**intubation**

- These patients will generally require CT scan, lumbar puncture, and MRI – the safest way to achieve this is often intubation.
- Patients may have elevated ICP, so there should be meticulous attention to:
  - Avoiding hypercapnia
  - Avoiding hypoxemia
  - Avoiding hypotension (ideally keep MAP >75 mm; more on this below)
- However, excessive deviation from your usual intubation practice may also cause errors. High-quality rapid sequence intubation by an experienced operator with attention to blood pressure is generally a reasonable approach.
- Immediately following intubation, titrate end tidal CO2 to 30mm. An ABG may be obtained 10-15 minutes later, targeting normocapnia (pCO2 35-45 mm).

\(^{1}\) John S and Khara R, 2016 PMID 26350907.

non-contrasted head CT

- The goal here is to exclude an alternative diagnosis (e.g. hemorrhage) and ensure that it’s safe to perform a lumbar puncture.
- There is some controversy about requirement for CT prior to lumbar puncture. However, this section refers to obtunded patients, who are recommended to receive a CT scan before lumbar puncture.

lumbar puncture with opening pressure

- Opening pressure is actually helpful in this scenario and should be measured. In a supine position, the opening pressure will equal the patient’s intracranial pressure (ICP). This can be converted from cm water to mm mercury using the following formula:
  
  ICP in mm = 0.7(Opening pressure in cm water)

- Obese patients may require ultrasound-guided lumbar puncture (videos of this are here and here).

Tests

- (a) Basics = protein, cell count with differential, glucose, gram stain & culture.
- (b) PCR for VZV & HSV.
- (c) Cryptococcal antigen if immunosuppressed.
- (d) Autoimmune encephalitis panel if suspicion for paraneoplastic or anti-NMDA receptor encephalitis.
  
  Hold additional uid for further tests PRN.

adjust MAP target to obtain adequate cerebral perfusion pressure (CPP)

- Cerebral perfusion pressure (CPP) = MAP − ICP
- A reasonable target CPP may be >60 mm (ideal target unknown, sources vary between 60-70 mm).
- For patients with unknown ICP targeting a generous MAP (e.g. >75 mm) may be reasonable.
- Once the ICP is known, MAP target can be adjusted accordingly:
  
  Target MAP > [65 mm + ICP]
  Target MAP > [65 mm + 0.7(lumbar puncture opening pressure measured in cm water)]
- Either norepinephrine or phenylephrine are reasonable to maintain MAP above target.

avoid fever

- There is no direct evidence for this in meningitis/encephalitis, but fever is generally harmful for neurocritically ill patients.
- Scheduled acetaminophen (1 gram Q6hr) is a good first step, but this is often ineffective.
- Physical cooling (e.g. arctic sun or ice packs) may be needed as well.

beware of seizures

- Seizures are common in severe meningitis and especially encephalitis. Seizure will make a bad situation much, much worse.
- If there is concern for non-convulsive status epilepticus, this should be excluded (e.g. with EEG).
- In absence of clear evidence, seizure prophylaxis may be reasonable (e.g., 1 gram levetiracetam PO/IV Q12 hours).

obtain a MRI with MR venography

- Patients with severely altered consciousness or focal findings need definitive neuroimaging with MRI if possible.
- There is a surprisingly high rate of abnormal findings which will alter management, including:
  
  Meningitis with sinus vein thrombosis (potentially requires anticoagulation).
  Brain abscess (can be initial focus of infection, may require surgery).
  Anatomic portals of entry causing meningitis (e.g., encephalocele causing CSF leak, otitis media with extension into the brain).
  Anatomic distribution of encephalitis may suggest various pathogens (e.g. temporal lobe involvement suggests HSV).

consider therapeutic drainage of CSF for patients with meningitis

- Patients with meningitis may benefit from therapeutic removal of CSF if they have the following:
  
  (a) Significantly elevated ICP (e.g. opening pressure >27 cm water).
  (b) Abnormal mental status.
CSF drainage may serve to reduce the ICP and also drain off infected material (“source control”).

Two ways of achieving CSF drainage:

(a) Lumbar drain placement by neurosurgery.
(b) Serial lumbar puncture (e.g. Q12 hr) with measurement of opening pressure, removal of ~20 ml, and measurement of closing pressure.

This is controversial: evidence discussed here.

CSF interpretation

CSF results can be grossly categorized into three patterns. Unfortunately, none of these patterns are highly specific for anything:

<table>
<thead>
<tr>
<th>Typical CSF patterns</th>
<th>Normal</th>
<th>Bacterial pattern</th>
<th>Viral pattern</th>
<th>Malignant/fungal pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opening pressure</strong></td>
<td>6-20 cm H2O</td>
<td>15-50 cm H2O</td>
<td>6-30 cm H2O</td>
<td>15-50 cm H2O</td>
</tr>
<tr>
<td><strong>CSF white count</strong></td>
<td>&lt;5 cells/μL</td>
<td>Lymphocyte predominant</td>
<td>Neutrophil predominant</td>
<td>Lymphocyte predominant</td>
</tr>
<tr>
<td><strong>CSF protein level</strong></td>
<td>(&lt;0.6 mg/dL)</td>
<td>80-500 mg/dL</td>
<td>Other</td>
<td>80-500 mg/dL</td>
</tr>
<tr>
<td><strong>CSF glucose</strong></td>
<td>&gt;40 mg/dL (2.2 mmol/L)</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

**correction for RBCs**

- Traumatic lumbar puncture will cause an increase in RBCs and WBCs, in a ratio equal to that present in the blood.
- An online calculator can be used to estimate the number of WBCs in the CSF prior to contamination with peripheral blood.

If a CBC isn't available, a very rough estimation is that 1,000 RBCs correlates to 1 WBC.

**bacterial pattern**

- Causes
  - Bacterial meningitis
  - Early meningeal response to any type of infection (early TB, fungal, viral, or drug-related meningitis).
  - Parameningeal focus of infection (brain abscess, subdural empyema, epidural abscess)

- Further evaluation
  - Some features are strongly suggestive of bacterial infection if present: glucose <34 mg/dL (1.9 mM), protein >220 mg/dL, CSF WBC count >2000/μL, CSF neutrophil count >1180/μL.
  - In borderline cases, it may be helpful to repeat lumbar puncture later on to determine if this is an early response which shifts to a lymphocyte-predominant pattern over time.

**viral pattern**

- Causes
  - Viral meningitis (e.g., enteroviruses, HSV, HIV)
  - Viral encephalitis
  - Partially treated bacterial meningitis
  - Listeria meningitis
  - Spirochetal infection (leptospirosis, lyme, syphilis)
  - Rickettsial infection (rocky mountain spotted fever, ehrlichiosis)
  - Drug-induced meningitis
  - Endocarditis
  - Paraneoplastic encephalomyelitis
SLE, multiple sclerosis, acute disseminated encephalomyelitis

Key point: A viral pattern doesn't mean that the patient just has "some virus" which requires no treatment.

malignant/fungal pattern

- Causes
  - Malignancy (leptomeningeal carcinomatosis)
  - Tuberculosis, fungal meningitis
  - Listeria
  - Lyme
  - CNS vasculitis, neurosarcoidosis
  - Lymphohorion meningitis virus (LCMV)

antibiotic selection

Most common agents of meningitis and encephalitis, and their relative annual frequency in the USA

<table>
<thead>
<tr>
<th>Organism</th>
<th>Cases/year in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial meningitis</strong></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>3000–6000 (CDC, 2015c)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>500–700 (CDC, 2015d)</td>
</tr>
<tr>
<td>Group B streptococcus (GBS)</td>
<td>Approximately 500 (Schuchat, 1998; CDC, 2015b)</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Approximately 250 (CDC)</td>
</tr>
<tr>
<td><strong>Viral encephalitis</strong></td>
<td></td>
</tr>
<tr>
<td>West Nile</td>
<td>1000–2500</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1250</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>Approximately 800</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>Approximately 500–600</td>
</tr>
</tbody>
</table>

Table from Halperin JJ 2017 PMID 28187808

what we're up against

- The frequencies of various diseases in the United States is shown above. A few points are notable:
  - (1) Varicella zoster (VZV) occurs with reasonable frequency and should be tested for alongside HSV (especially because it's treatable).
  - (2) Autoimmune encephalitis is rather common, and should also be routinely considered.
    - Ordering an autoimmune encephalitis panel is generally more useful than ordering $5,000 worth of tests for every untreatable virus known to humankind.
  - (3) Listeria isn't terribly common (accounting for 2% of all comers with encephalitis meningitis; more on this below).

three-drug regimen for possible CNS infection (before lumbar puncture)

- For patients with possible CNS infection, a three-drug regimen may be reasonable (ceftriaxone 2 grams IV, acyclovir 10 mg/kg IV, and dexamethasone 10 mg IV).
- Many practitioners will use a five-drug regimen here (including vancomycin and ampicillin). Immediate administration of vancomycin and ampicillin is probably unnecessary for the following reason:
  - The only reason to use vancomycin is for highly drug-resistant pneumococcus, whereas the only reason to use ampicillin is for listeria. Both of these pathogens are rare when we consider all patients with encephalitis meningitis (~2% or less; see table above).
  - Among patients with possible CNS infection, most of these patients won't actually end up having any CNS infection at all. At most, perhaps ~20% of such patients have a CNS infection.
Multiplying 20% by 2% indicates that the likelihood that a patient with possible CNS infection has listeria or highly drug-resistant pneumococcus is <0.5%.

Patients should get a lumbar puncture within a few hours, so antibiotics can be broadened further if the results suggest bacterial infection.

### Specific antibiotic in-hospital treatment for community-acquired bacterial meningitis

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Standard treatment</th>
<th>Alternatives</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumonia</em>&lt;br&gt;Penicillin susceptible (MIC &lt;0.1 µg/mL)</td>
<td>Penicillin or amoxicillin/ampicillin</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Penicillin resistant (MIC &gt;0.1 µg/mL)</td>
<td>Ceftriaxone or cefoxitin</td>
<td>Ceftriaxone, meropenem, moxifloxacin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Third-generation cephalosporin susceptible (MIC &lt;2 µg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporin resistant (MIC ≥2 µg/mL)</td>
<td>Vancomycin plus rifampicin, or vancomycin plus ceftriaxone or cefoxitin, or rifampicin plus ceftriaxone or cefoxitin&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>10–14 days</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em>&lt;br&gt;Penicillin susceptible (MIC &lt;0.1 µg/mL)</td>
<td>Penicillin or amoxicillin/ampicillin</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol</td>
<td>7 days</td>
</tr>
<tr>
<td>Penicillin resistant (MIC &gt;0.1 µg/mL)</td>
<td>Ceftriaxone or cefoxitin</td>
<td>Ceftriaxone, meropenem, moxifloxacin&lt;sup&gt;1&lt;/sup&gt;, linezolid</td>
<td>7 days</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxicillin or ampicillin, penicillin G&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol, moxifloxacin&lt;sup&gt;3&lt;/sup&gt;, meropenem, linezolid</td>
<td>At least 21 days</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em>&lt;br&gt;β-Lactamase negative</td>
<td>Amoxicillin or ampicillin</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol</td>
<td>7–10 days</td>
</tr>
<tr>
<td>β-Lactamase positive</td>
<td>Ceftriaxone or cefoxitin</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol</td>
<td>7–10 days</td>
</tr>
<tr>
<td>β-Lactamase negative ampicillin resistant</td>
<td>Ceftriaxone or cefoxitin plus meropenem</td>
<td>Ceftriaxone, cefoxitin, chloramphenicol</td>
<td>7–10 days</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>&lt;br&gt;Methicillin sensitive</td>
<td>Flucloxacillin, nafcillin, oxacillin</td>
<td>Vancomycin, linezolid, rifampicin&lt;sup&gt;1&lt;/sup&gt;, fosfomycin&lt;sup&gt;2&lt;/sup&gt;, daptomycin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>At least 14 days</td>
</tr>
<tr>
<td>Methicillin resistant</td>
<td>Vancomycin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Fosfomycin&lt;sup&gt;2&lt;/sup&gt;, daptomycin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>At least 14 days</td>
</tr>
<tr>
<td><em>Vancomycin resistant (MIC ≥2.0 µg/mL)</em></td>
<td>Linezolid&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Rifampicin&lt;sup&gt;1&lt;/sup&gt;, fosfomycin&lt;sup&gt;2&lt;/sup&gt;, daptomycin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>At least 14 days</td>
</tr>
</tbody>
</table>

<sup>1</sup>Recommendations must be in accordance with the results of the susceptibility testing.

<sup>2</sup>Based on case reports.

<sup>3</sup>Ceftriaxone dose 2 g q12h and cefoxitin 2–3 g q8h.

<sup>4</sup>Adding an aminoglycoside can be considered.

<sup>5</sup>Must not be used in monotherapy.

<sup>6</sup>Addition of rifampicin can be considered.

**Empiric treatment for meningitis/encephalitis with bacterial-pattern**

- Treatment involves a cocktail of several drugs
  - (1) Dexamethasone 10 mg IV q6hr for four days.
  - (2) Ceftriaxone 2 grams IV q12hr.
    - If the patient has a history of penicillin anaphylaxis or cephalosporin allergy, may use meropenem 2g IV q8hr.
  - (3) Listeria coverage in patients >50YO, pregnant, or immunocompromised (e.g. diabetes, immunosuppressive drugs, cirrhosis, malignancy).
  - Usual coverage is ampicillin 2 grams IV q4hours. However, ampicillin isn’t required for patients on meropenem (which covers Listeria).
  - (4) Cephalosporin-resistant pneumococcus coverage
    - Generally provided, although it may not be needed if there is a low local incidence of cephalosporin-resistant pneumococcus.<sup>3</sup>
    - Either vancomycin or rifampicin may be used for this, in conjunction with ceftriaxone.<sup>2</sup> For patients at risk of acute kidney injury, rifampicin might be safer (600 mg q12hr). Rifampicin may also offer some anti-inflammatory effects and superior meningeal penetration.<sup>3</sup>

**Empiric treatment for meningitis/encephalitis with viral-pattern**

- Dexamethasone and most anti-bacterial therapies may be discontinued. Treatment involves the following:
  - (1) Acyclovir 10 mg/kg q8hr should be continued until HSV & VZV PCR results are returned:
    - If there is a very high suspicion for HSV encephalitis (e.g. based on MRI with temporal enhancement) and HSV PCR is negative, repeat the HSV PCR. False-negative PCR is possible during the first 72 hours after onset.<sup>9</sup>
    - Discontinuation of acyclovir is explored in detail [here](https://emcrit.org/pulmcrit/hsv-coverage/) and summarized in the algorithm below.
  - (2) Listeria can have a viral pattern, so listeria coverage might be considered in patients at risk for this (e.g. older/immunocompromised).
  - (3) Consider doxycycline 100 mg twice daily if rocky mountain spotted fever or tick-borne encephalitis is possible.
Obtunded/comatose patient with suspected meningitis/encephalitis

- **Droplet precaution**: if meningococcal meningitis is a possibility.
- **Labs**
  - Fingerstick glucose
  - Lytes, CBC, coagulation studies
  - Blood cultures x2
  - HSV screen if this is a possibility
- **Empic therapy**
  - Dexamethasone 10 mg IV
  - Ceftriaxone 2 grams IV (or meropenem 2 grams IV if PCN anaphylaxis/cephalosporin allergy)
  - Acyclovir 10 mg/kg IV
- **D/C DVT prophylaxis** (to facilitate LP – make sure this isn’t ordered as part of ICU admission set orders)
- **Head CT scan**
- **LP**
  - Measure opening pressure
  - Target MAP > [60 + 0.7(Opening Pressure in cm)]
- **MRI/MRV if possible**
  - For patient with significantly altered mental status, obtain MRI (unless impossible, e.g. pacemaker)
  - Will generally require intubation to stabilize airway before MRI
  - Obtain MR venogram (MRV) along with MRI (meningitis carries significant risk of venous sinus thrombosis)
- **Fever prevention/treatment**
  - Acetaminophen 1000 mg PO q6hr scheduled
  - Cooling blankets or arctic sun if needed to achieve normothermia
- **Seizure control**
  - If concern for seizure, obtain EEG
  - Consider levetiracetam for sx prophylaxis in severe CNS infection

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**podcast**


Failure to give steroid along with antibiotic. Steroid is recommended by both US and European guidelines, based on prospective RCTs proving reduction in long-term neurologic disability.

Under-utilization of ultrasound-guided lumbar puncture for morbidly obese patients (if you’re sending patients for IR-guided lumbar puncture, consider ultrasound).

Delaying steroid/antibiotic therapy (e.g. for lumbar puncture, blood cultures, etc.).

Failing to check VZV PCR (this is seen occasionally, so if you’re going to get HSV PCR it’s worth getting VZV also).

Keep in mind that antibiotics often require higher doses to penetrate the meninges (“meningeal dose”). Thus, simply because the patient is on an antibiotic doesn’t mean that meningitis is necessarily covered adequately.

Recognize that a patient with meningitis/encephalitis and obtundation is critically ill, and should usually receive care in an ICU.

Going further:

- [Neurocritical care of the comatose meningitis patient](https://emcrit.org/pulmcrit/neurocritical-care-meningitis-icp/#comment-268272) (PulmCrit)
- [Severe CNS Infections](https://emcrit.org/emcrit/severe-cns-infections/) (EMCrit)
- [Meningitis Pearls & Pitfalls](http://www.emdocs.net/meningitis-clinical-pearls-pitfalls/) (Aaron Tiffee and Marc Zosky, emDocs)
- [Bacterial Meningitis, Encephalitis](https://lifeinthefastlane.com/ccc/bacterial-meningitis/), [anti-NMDA receptor encephalitis](https://lifeinthefastlane.com/ccc/anti-nmda-receptor-encephalitis/), [HSV encephalitis](https://lifeinthefastlane.com/ccc/hsv-encephalitis) (Chris Nickson, LITFL)
- [Neurocritical care intubation](https://emcrit.org/podcasts/neurocritical-care-intubation/) (EMCrit)

References:


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.