APPROACH TO INFECTIOUS ENCEPHALITIS AND MENINGITIS

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Encephalitis and meningitis should be considered in any patient with altered mental status and fever; however, note that septic *encephalopathy* from a non-CNS source of an infection is more common than *encephalitis*.

Encephalitis and meningitis are diagnosed when there is evidence of inflammation in the brain parenchyma or meninges, respectively. This requires evidence of inflammation in the CSF (pleocytosis => 5 cells/mm3) and/or an abnormality on neuroimaging (as some immunocompromised hosts or certain infections may not result in significant pleocytosis).

Signs that increase concern for meningitis / encephalitis include:	Host Factors that increase risk for CNS infection:	Extrinsic factors that may increase risk for CNS infection
- Fever - Headache - Nuchal rigidity - Altered mental status - Photophobia Patients may also present with: - Hydrocephalus - Seizures - Coma - Photophobia - Nausea/vomiting Note that elderly and immunosuppressed patients may have atypical presentations and no fever or neck rigidity	- Older age (>65 years old) - Transplant recipient or on immunosuppression for autoimmune condition - Active malignancy and/or cancer treatment - HIV+, or other acquired/ inherited immunodeficiency - Prior CNS surgical procedure - CSF leak - Recent traumatic brain injury - External ventricular drain	- Season (increased risk for mosquito or tick associated illness in summer) - Travel - Geographic origin

Workup[1]:

[ ] CBC and PT/INR/PTT/Anti-Xa STAT to evaluate for thrombocytopenia and/or coagulopathies which may impact ability to safely perform lumbar puncture (LP)

[ ] Blood cultures STAT

[ ] CT scan should strongly be considered before LP; mandatory for patients who are immunocompromised, >60 years old, have known CNS lesions, seizure on presentation or recently, abnormal level of consciousness, focal neurologic findings, papilledema.

[ ] LP. For procedural guidance see page ##, for test ordering guidance, see page ##. Consider in all patients:

- Cell count, Tube 1 and Tube 4
- Tube 2: Total protein, glucose
- Tube 3: CSF gram stain and culture
- Empiric HSV PCR testing should be considered in all patients as it is common and treatable
- Biofire® ME Panel can be considered; hospital policies differ on who qualifies for this test. Shown in a multicenter prospective study to have 84.4% positive and >99.9% negative agreement between conventional methods.[2] However, note that cryptococcal antigen is much more sensitive than the Biofire test for this agent.
- Other studies should be guided by patient's risk factors, clinical / radiographic syndrome, and exposures. See page ##.

CNS Biofire FilmArray
Bacterial pathogens
- *Escherichia coli* K1,
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Viral Pathogens
- Cytomegalovirus (CMV),
- Enterovirus (EV),
- Herpes simplex virus 1 (HSV-1),
- HSV-2,
- Human herpesvirus 6 (HHV-6)
- Human parechovirus (HPeV)
- Varicella-zoster virus (VZV)

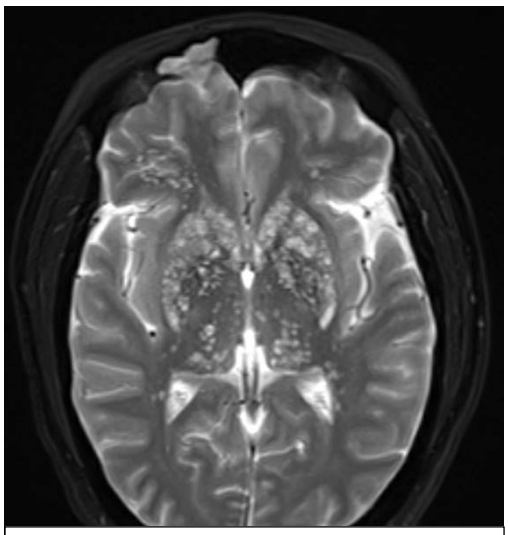
Yeast
- *Cryptococcus neoformans/ Cryptococcus gattii.*

[ ] MRI with and without gadolinium should be obtained urgently, but not before the patient has been resuscitated and started on broad spectrum antimicrobials.

- MRI can be used to evaluate for meningeal and brain parenchymal enhancement, indicate patterns of edema (eg limbic encephalitis vs rhombencephalitis), or demonstrate other anatomic findings suggestive of a specific disease pathology (eg dilated Virchow-Robin spaces in cryptococcal meningitis (see image).)[3]

[ ] Consider continuous EEG monitoring in patients with fluctuating or depressed consciousness

Although risk of herniation is not precisely known, LP should be deferred in cases with evidence of transtentorial or uncal herniation, shift or compression of 4th ventricle, midline shift, cerebellar mass, obstructive hydrocephalus



MRI T2 weighted image demonstrating dilated Virchow-Robins spaces throughout the basal ganglia and thalamus in a patient with cryptococcal meningitis.

[1] Venkatesan, Arun, et al. "Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium." *Clinical Infectious Diseases* 57.8 (2013): 1114-1128.

[2] Leber, Amy L., et al. "Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens." Journal of clinical microbiology 54.9 (2016): 2251-2261.

[3] Berkefeld, J., W. Enzensberger, and H. Lanfermann. "Cryptococcus meningoencephalitis in AIDS: parenchymal and meningeal forms." Neuroradiology 41.2 (1999): 129-133.

Typical CSF Findings in Infectious Meningitis

	Total Nucleated Cell Count	Protein	Glucose
Bacterial Meningitis	1000-3000, neutrophilic predominance	Very Elevated	Very low. Less than 2/3 serum glucose. Often <25 mg/dL
Viral Meningitis *HSV encephalitis may have increased red blood cells in CSF	200- >1000, lymphocytic although may be neutrophilic early in disease	Mildly elevated	Normal, although may be low in some cases
Fungal Meningitis	100-500	Very elevated	Low

Treatment:
Do not delay starting treatment to get neuroimaging/LP. Draw blood cultures and then start treatment while arranging for imaging and LP. Most antibiotics result in CSF sterilization within 4 hours; however, *Neisseria Meningitidis* may be sterilized in 30 mins after effective antibiotics.

HSV PCR and Treatment:
If moderate suspicion for HSV encephalitis and PCR negative, do not stop treatment. Per IDSA guidelines, continue treatment, resend CSF HSV PCR in 3-7 days.

Empiric Treatment for Community Acquired Meningitis/Encephalitis:

- Vancomycin (dosed by weight and renal function)
- Ceftriaxone 2g Q12H (May consider alternative 3rd/4th generation cephalosporin)
- Acyclovir 10mg/kg Q8H unless clinically there is no concern for HSV encephalitis
- Ampicillin 2g IV Q4H for *Listeria monocytogenes* if >50 years old or immunocompromised.
- If high concern for bacterial (particularly *Streptococcal pneumoniae* meningitis), give Dexamethasone 10mg IV about 10 minutes prior to first dose of antibiotics. And continue 48-96 hours if proven bacterial/*S. pneumoniae* infection

If healthcare associated ventriculitis/meningitis (CNS drains, neurosurgery, head trauma)[4]:	**If concern atypical infections (B*rucella, Mycoplasma, ricettsiosis, Ehrlichiosis*):**	**Patients with Penicillin Allergies:**
Use vancomycin + a pseudomonal-active 3rd or 4th generation cephalosporin (ceftazidime vs cefepime) or meropenem; remember that these patients are at higher risk for fungal meningitis and Infectious disease guidance is helpful in determining treatment and explant of potentially infected hardware, as applicable.	Doxycycline 100mg PO or IV Q12H	**Vancomycin PLUS** **IgE-mediated reaction (e.g. anaphylaxis, angioedema, hives/urticara):** Aztreonam (+ TMP/SMX if listeria coverage required) Meropenem (has listeria coverage)

[4] Tunkel, Allan R., et al. "2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis." Clinical Infectious Diseases 64.6 (2017): e34-e65.

		Severe penicillin allergy (e.g. SJS/TENs, DRESS, hemolytic anemia): Vancomycin + Fluroquinolone + TMP/SMX (if indicated for listeria coverage)

CNS Penetration of Commonly Used Antibiotics

Drug	**CNS % Penetration**	**Empiric dosing if CrCl > 50 mL/min** **Dose adj may be required if poor renal fxn**
Penicillin G	Moderate	4 million units IV q4h
Ampicillin	Moderate	2g IV q4h
Nafcillin	Moderate	2g IV q6h
Piperacillin/tazobactam	Poor	Do not use for CNS infections
Cefazolin	Low	Do not use for CNS infections
Ceftriaxone	Moderate	2g IV q12h
Ceftazidime	Moderate	2g IV q8h
Cefepime	Moderate	2g IV q8h
Meropenem	Good	2g IV q8h
Ciprofloxacin	Excellent	400 IV q8h
Levofloxacin	Excellent	750 IV 24h
Doxycycline	Moderate	Lyme meningitis only
Vancomycin	Poor to Moderate	See vancomycin dosing, page 21
Linezolid	Excellent	600 IV q12h
TMP/SMX	Moderate-Good	15-20 mg/kg/day divided q6-8h
Metronidazole	Good	500 IV q6-8h
Acyclovir	Good	10 mg/kg IV q8h

Sample Vancomycin Dosing Recommendations:

Loading dose (ALL patients)	CrCl > 80 mL/min AND Age < 65	CrCl 40 – 80 mL/min or Age > 65	CrCl 39 – 39 mL/min	CrCl 20 – 29 mL/min	CrCl < 20 mL/ min, AKI, or labile renal fxn	CRRT or IHD
20 – 25 mg/kg	15 mg/kg q8h	15 mg/kg q12h	15 mg/kg q24h	15 mg/kg q24-q48h	Discuss with pharmacy, dose by level	Discuss with pharmacy, dose by level

Subtherapeutic 1st level within 10% of goal	Continue same dose with expected accumulation
Level < 5 mcg/mL from goal	Increase each dose by 250 mg
Level > 5 mcg/mL lower than goal	Modify dosing interval to next shorter interval (e.g. q12h to q8h)
Supratherapeutic 21 – 25 mcg/mL	Hold next dose until level is expected to be within target then ↓dose by 250 mg/dose or 500 mg/day
26 – 30 mcg/mL	Hold dose, repeat random vancomycin level to inform dosing
> 30 mcg/mL	Hold dose, re-initiate when random level within target range. Consult Rx for dose recommendations