Central Nervous System Infections: Updates in Literature & Treatment

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Conflicts of Interest
No financial or professional conflicts of interest to disclose

Objectives
- Identify antimicrobial medications commonly used in the treatment of central nervous system (CNS) infections
- Compare the recommendations from the new 2017 IDSA guidelines for healthcare-associated meningitis and ventriculitis to content previously published in the 2004 meningitis guidelines
- Describe ways to optimize the efficacy of pharmacologic treatment of CNS infections

Review of Anatomy: the Brain
- Cerebrum or Cerebral Cortex (Latin, “the brain”)
- Encephalon (Greek, “what is inside the head”)

Anatomy: the Meninges
- Membranes between the brain and the skull

Layers of the Meninges
- Periosteal
- Dura mater
- Arachnoid mater
- Pia mater
- Arachnoid villus
- Blood vessels
Anatomy: Ventricles and the Cerebrospinal Fluid (CSF)


Infections of the CNS
- **Encephalitis**: inflammation/infection of the brain
- **Meningitis**: inflammation/infection of the CNS, centered around the meninges
- **Meningoencephalitis**: features of both the above
- **Ventriculitis**: inflammation of the lining of the ventricles/ventricular drainage system
- **CNS Abscesses**: Subdural, Epidural, Brain Abscesses

Pertinent IDSA Guidelines
- **Bacterial Meningitis (2004)**
- **Nervous System Lyme Disease (2007)**
- **Viral Encephalitis (2008)**
- **Management of Cryptococcal Disease (2010)**
- **Healthcare-Associated Ventriculitis and Meningitis (2017)**

Review of Bacterial Meningitis
- Presentation: Headache, Neck pain, Altered mental status, nonspecific signs: Fever, WBC, malaise, etc
- **Common pathogens**
  - *Listeria monocytogenes*
  - *Group B Streptococcus*
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
  - *Streptococcus pneumoniae*
- Incidence decreasing
- **Mortality**
  - 16.4-18% (adults)
  - 6.3-6.9% (pediatric)
Meningitis Diagnostic Workup

1. Suspicion of Meningitis
2. Blood Cultures, Lumbar puncture, CSF culture and gram stain STAT *
3. Empiric therapy
4. Continue therapy if CSF findings are consistent with meningitis or high clinical suspicion remains

* Delay LP if concern for elevated ICP and possible subdural herniation

Examining the CSF

- (+) Gram Stain: 60-90% sensitivity, 97% specificity
- Typical CSF chemistry findings

<table>
<thead>
<tr>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated &gt;50 mg/dL</td>
</tr>
</tbody>
</table>

- Glucose: < 67% CSF: Blood & commonly < 40%
- RBC: Normal, 0-5 cells/µL
- WBC: high, >500 cells/µL - Mostly Neutrophils

Bacterial Meningitis
- Protein: Elevated >50 mg/dL
- Glucose: < 67%
- RBC: Normal, 0-5 cells/µL
- WBC: high, >500 cells/µL - Mostly Neutrophils

Viral Meningitis
- Protein: Mild elevation
- Glucose: Normal >67%
- RBC: Normal (slight elevation if HSV)
- WBC: 10s-100s - Lymphocytes

Fungal Meningitis
- Protein: Elevated
- Glucose: Low
- RBC: Normal
- WBC: ~100-400 - Lymphocytes

- CSF Blood Glucose < 0.4: 80% sensitive, 98% specific
- CSF Lactate > 3.5 mmol/L: 93% sensitive, 96% specific in distinguishing bacterial from aseptic meningitis

Examining the CSF

Examining the CSF

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- CSF Lactate > 3.5 mmol/L: 93% sensitive, 96% specific in distinguishing bacterial from aseptic meningitis

Meningitis; Empiric Therapy

<table>
<thead>
<tr>
<th>Pathogens by Age</th>
<th>Common bacterial pathogens</th>
<th>Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>S. pneumoniae, Neisseria meningitidis, E. coli</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
<tr>
<td>1-2 months</td>
<td>S. pneumoniae, Neisseria meningitidis, E. coli</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
<tr>
<td>3-6 months</td>
<td>S. pneumoniae, H. influenzae, group A beta-hemolytic streptococcus</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
<tr>
<td>9-18 months</td>
<td>S. pneumoniae, H. influenzae, group A beta-hemolytic streptococcus</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
<tr>
<td>2-5 years</td>
<td>S. pneumoniae, H. influenzae, group A beta-hemolytic streptococcus</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
<tr>
<td>6-12 years</td>
<td>S. pneumoniae, H. influenzae, group A beta-hemolytic streptococcus</td>
<td>Amoxicillin plus clavulanate or ampicillin plus sulbactam or vancomycin plus a third generation cephalosporin</td>
</tr>
</tbody>
</table>

- Highest safe dosage to penetrate the blood brain barrier
  - Ceftriaxone 2 grams every 12 hours
  - Vancomycin to target troughs 15-20 mcg/mL

Audience Participation

- How many of you had at least one lecture in pharmacy school focusing on bacterial meningitis?
- How many of you had at least one lecture in pharmacy school focusing on healthcare-associated bacterial meningitis?
Audience Participation

What percentage of all meningitis cases are healthcare-associated?

A. 10%
B. 20%
C. 30%
D. 40%

Audience Participation

What percentage of all meningitis cases are healthcare-associated?

A. 10%
B. 20%
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Healthcare-associated Meningitis

Epidemiological data lacking
Institutional reviews of meningitis cases
- Mass General, 1962-1988, 493 cases, 40% nosocomial
- South Taiwan, 1986-2003, 329 Cases: 48% nosocomial
  Similar results for causative organisms

Organism | Community | Nosocomial
---------|-----------|-----------
Streptococci, H. influenzae, N. meningitides, L. monocytogenes | 64% | 8%
Staphylococci | 3% | 22%
Other Gram Negative Bacilli | 0% | 46%

New Guidelines!

Healthcare-associated Meningitis & Ventriculitis

“Meningitis may be acquired in the community setting or associated with a variety of invasive procedures or head trauma”

- Neurosurgical hardware to be considered
- May become symptomatic during hospitalization, may develop after discharge or months/years later
- Different pathogens predominate

http://raczpainmanagement.com/intrathecal-pain-pump-therapy

Intrathecal medication pump
Ventriculoperitoneal shunt
External ventricular Drain (EVD)
Deep Brain Stimulator (DBS)
Epidemiology: Pathogens

- Decreasing incidence of “typical” pathogens historically seen in meningitis
- Higher proportion of cases caused by:
  - Staphylococci: *S. aureus, S. epidermidis*
  - Propionibacterium acnes
  - Gram negative bacilli, including MDR organisms:
    - *P. aeruginosa*
    - *E. coli*
    - *Klebsiella* species
    - *Serratia* species
    - *Citrobacter, Enterobacter, Acinetobacter* species

**Diagnostic Factors**

- Diagnosis MUCH less straightforward than community cases
  - Pathogens more indolent
  - Symptomatology more subtle, varying with disease state
  - Concomitant disease states cloud the picture
- Signs of meningeal irritation typically absent
  - 30% of patients or less
- Does it look like an infection?
  - Yes? → Probably an infection
  - No? → Still might be

**Diagnostic: CSF Chemistries**

- Also may be unreliable for diagnosis
  - Schade et al. 2006: 230 patients with external ventricular drains (EVDs):
    - Daily CSF sampling for chemistries and cultures
    - 22 patients developed ventriculitis and/or meningitis
    - Nonsignificant: WBC count, protein, CSF : Blood glucose
- Most likely to be reliable: CSF WBC count
  - Walti et al. 2013: WBC count >175 cells/µL predictive of infection
  - All other parameters showed nonsignificant results
  - Pfisterer et al. 2003: CSF WBC count correlates with positive CSF culture results
    - Median values = 150 - 237 cells/µL

**Diagnostic: CSF Cultures**

- Most reliable means of diagnosis, per 2017 guidelines
  - “Single or multiple positive CSF cultures in patients with... other signs or symptoms... suspicious for ventriculitis or meningitis, is indicative of CSF drain infection (strong, high)"
- CSF cultures usually sensitive and specific for infection

- Other recommendations:
  - Obtain CSF cultures
  - Hold cultures for 10 days in case of *P. acnes*
  - If hardware infection suspected, culture shunt and drain components
  - Obtain CSF and blood cultures prior to giving antibiotics

**Empiric Treatment**

- Minimal expansion on the 2004 recommendations
- First line empiric regimen:
  - Vancomycin + cefazidime or cefepime or meropenem
- Second line against GNRs:
  - If patient has anaphylaxis to β-lactams AND meropenem is contraindicated: ciprofloxacin or aztreonam
- Second line against gram positive bacteria:
  - No alternatives to vancomycin mentioned in the guidelines
  - Reasonable options:
    - Daptomycin, Linezolid, or Sulfamethoxazole-Trimethoprim (SMX-TMP)
- Note: all recommendations are “strong” recommendations with “low” quality of evidence (i.e. expert consensus)

**Patient Case**

- Patient X: 52 yo F, no PMH or medications
  - No known drug allergies
  - Presents to outside ED with thunderclap HA and vomiting. Head CT shows SAH with ventricular extension
  - Transferred to our facility, CT angiogram confirms diagnosis, pinpoints an ACOMM aneurysm rupture
Patient X

Hospital day 1:
- Emergent Coiling of the ACOMM aneurysm and placement of an EVD on hospital day 1, admitted in stable condition to Neuro ICU

Hospital day 9:
- Temp 102.5°F
- WBC 17.5 K
- CSF chemistries →
- BG 119

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cell Count - CSF</td>
<td>14,000 K</td>
</tr>
<tr>
<td>Red Blood Cell Count - CSF</td>
<td>4,500 K</td>
</tr>
<tr>
<td>Neutrophils - CSF</td>
<td>87 %</td>
</tr>
<tr>
<td>Lymphocytes - CSF</td>
<td>9 %</td>
</tr>
<tr>
<td>Monocytes - CSF</td>
<td>4 %</td>
</tr>
<tr>
<td>Glucose - CSF</td>
<td>95 mg/dL</td>
</tr>
<tr>
<td>Protein - CSF</td>
<td>21 mg/dL</td>
</tr>
</tbody>
</table>

Assessment Question

What is the appropriate empiric antibiotic regimen for Patient X?
A. Vancomycin + Ceftriaxone
B. Vancomycin + Cefepime
C. Vancomycin + Gentamicin
D. Daptomycin + Meropenem

Assessment Question

What is the appropriate empiric antibiotic regimen for Patient X?
A. Vancomycin + Ceftriaxone
B. Vancomycin + Cefepime initiated 1250 mg Q12h 2 grams Q8h
C. Vancomycin + Gentamicin
D. Daptomycin + Meropenem

Pathogen-Specific Treatment

Note: no randomized clinical trial data available. All recommendations based on observational studies, case series, and expert opinion
Pathogen-Specific Treatment

Gram Positives

Staphylococcus
- Methicillin-Sensitive: Nafcillin or Oxacillin
  Alternative: vancomycin
- Methicillin-Resistant: Vancomycin
- Alternatives: daptomycin, linezolid, SMX-TMP

P. acnes
- First line therapy: Penicillin G
  Alternatives: ceftriaxone, vancomycin, daptomycin, or linezolid

S. pneumoniae
- If Penicillin MIC ≤ 0.06 mcg/mL: penicillin G
  Alternative: ceftriaxone
- If Penicillin MIC ≥ 0.12 mcg/mL: ceftriaxone
  Alternative: cefepime or meropenem
- If Ceftriaxone MIC ≥ 1 mcg/mL: vancomycin + ceftriaxone
  Alternative: add moxifloxacin to ceftriaxone or vancomycin

Evidence Summary

Gram Positives

Staphylococcus infections:
- If vancomycin MIC ≥ 1 mcg/mL, consider alternatives
  Linezolid, daptomycin, SMX-TMP
- Source: IDSA guidelines for MRSA (2011), no further data cited
- Consider adding rifampin
- Especially when hardware involved
- Enhances the bactericidal activity of the primary agent
- Evidence very limited and outdated

Evidence Summary

Gram Negatives

P. aeruginosa
- 1st line: ceftazidime, cefepime, or meropenem
  Alternatives: ciprofloxacin or aztreonam

Acinetobacter baumannii
- 1st line: meropenem
  Alternatives: colistin or polymyxin B

H. influenzae
- β-Lactamase (-): ampicillin
  Alternatives: ceftriaxone, cefepime, or a FQ
- β-Lactamase (+): ceftriaxone
  Alternatives: aztreonam, cefepime, or a FQ

ESBL-producing organisms
- 1st line: meropenem
  Alternatives: cefepime or a FQ
- For enterobacteriaceae that hyperproduce ESBLs (Enterobacter, Citrobacter, Serratia species), meropenem or SMX-TMP may be preferred

Enterobacter species:
- Questionable efficacy of some Beta-lactam agents
  - 1993 review of 46 enterobacter meningitis cases
    - 100% cure rate with SMX-TMP
    - 70% with beta-lactam agents
  - Possible treatment-emergent resistance to ceftriaxone?
  - 2005 retrospective review of 19 cases
    - 81% cure rate with SMX-TMP
    - 54% with 3rd generation cephalosporins
Patient Case, revisited

- **Review:**
  - SAH s/p coiling & EVD placement for hydrocephalus/CSF drainage
  - Probable meningitis/ventriculitis on hospital day 9
  - Empiric antibiotics (Vancomycin + Cefepime) started

**Hospital day 11**
- Persistent Fever to 102.6°F, WBC 18.4
- Initial day 9 CSF Culture results:
  - Day 11 CSF chemistries:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSF</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5</td>
<td>✓</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt;75</td>
<td>✓</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&lt;25</td>
<td>✓</td>
</tr>
<tr>
<td>Protein</td>
<td>305</td>
<td>✓</td>
</tr>
<tr>
<td>Glucose</td>
<td>65</td>
<td>✓</td>
</tr>
</tbody>
</table>

- Cefepime is deescalated appropriately to Ceftriaxone.
- Vancomycin is discontinued

Assessment question

- **True/False:** Patient X is responding appropriately to sufficient antibiotic therapy
  - A. True
  - B. False

**Clinical signs (high fever, leukocytosis) and CSF chemistries indicate suboptimal response**

Assessment question

- **What strategies could maximize bactericidal activity and patient response?**
  - A. Add Sulfamethoxazole-Trimethoprim for synergy
  - B. Add intraventricular Ceftriaxone
  - C. Add intraventricular Gentamicin
  - D. Go for broke and reescalate antibiotics to Daptomycin + Meropenem + Colistin + Azithromycin

**Intraventricular therapy appropriate, IVT Ceftriaxone contraindicated due to high incidence of seizures with intraventricular Beta-lactams**

**The Blood Brain Barrier**

1. Tight junctions between vascular endothelial cells
2. Additional lipid basement membrane
Pharmacokinetic Considerations

- [CSF] / [Serum] ~5-20% for most agents

Factors influencing CNS Penetration
- Smaller molecular size = better penetration
- More lipophilic drugs = better penetration
- Protein binding: higher free drug fraction = better
- Meningeal inflammation = better penetration
- Active transport/Active clearance
  - P-GP, OAT3, PEPT2 transporter proteins
  - Negligible effects for most commonly used agents

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  - P-GP, OAT3, PEPT2 transporter proteins
  - Negligible effects for most commonly used agents

Drug Penetration into the CNS

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>CSF AUC/Serum AUC (%) Un-inflamed meninges</th>
<th>CSF AUC/Serum AUC (%) Inflamed meninges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>0.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Penicillins</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>5.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Cefepime</td>
<td>N/A</td>
<td>10.3</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.8-11.5</td>
<td>N/A</td>
</tr>
<tr>
<td>TMP-Sulfa</td>
<td>12-18</td>
<td>24-51</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>14-18</td>
<td>38</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Rifampin</td>
<td>22</td>
<td>N/A</td>
</tr>
<tr>
<td>Meropenem</td>
<td>5-25</td>
<td>39</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>N/A</td>
<td>87</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2-43</td>
<td>92</td>
</tr>
<tr>
<td>Ertapenecil</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Linezolid</td>
<td>80</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Intraventricular Drug Administration

- External Ventricular Drain (EVD)
  - Most common method of IVT
  - Frequently already in place

- Ommaya Reservoir
  - May be preferable for longer-term therapy

Benefits
- Bypasses the BBB; higher CSF [drug] than IV therapy
- Long CSF half-lives, once daily administration
- Minimal systemic toxicity

Risks and considerations
- NOT FDA-approved; off label usage
- Highly invasive
- Requires small volume, preservative-free formulations
- Variable neurologic toxicities
  - Hearing loss, seizures, tinnitus, headache

Intraventricular Antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Daily Intraventricular Dose (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>5-50 mg (usual 30 mg)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1-4 mg (usual 5 mg)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>5-20 mg (usual 5-10 mg)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5-20 mg</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2-10 mg</td>
</tr>
<tr>
<td>Collistimethate Sodium</td>
<td>10 mg</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>5 mg</td>
</tr>
<tr>
<td>Amphoterin B deoxycholate</td>
<td>0.01-1 mg</td>
</tr>
</tbody>
</table>

Dosing strategies
- May target CSF Trough concentrations 10-20x the Pathogen’s MIC
- May tailor dose and interval based on troughs, ventricle size, and EVD output

Images courtesy of SUNY-Stony Brook & Memorial Sloan-Kettering Cancer Center
Duration of Therapy

- Depends on the pathogen
  - *P. acnes* and coagulase-negative staphylococci
    - 10-14 days
  - *S. aureus* and Gram Negative Bacilli
    - 10-14 days (some experts would propose 21 days for GNR)
- Other considerations
  - If repeatedly positive CSF cultures:
    - 10-14 days from the last positive culture
  - If new CSF shunts or hardware to be re-implemented:
    - may require 7-10 days of negative CSF cultures prior to surgery
- No benefit to extended courses of treatment

Patient Case, revisited

- Optimizing therapy, Hospital Day 11
  - Ceftriaxone dosed 2 grams IV every 12 hours (maximum dose)
  - Intraventricular Gentamicin was added, 5 mg daily
- Clinical Course

Summary

- CNS infections pose unique challenges for physicians and pharmacists
- Healthcare-associated infections require specialized management
- Pharmacists’ skill sets make us uniquely positioned to optimize the treatment of difficult-to-manage cases

Questions

Contact Info: brett.vanrossum@bmcjax.com

References:


References: (continued)


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