

Clinical Practice Guideline Updates for Central Nervous System Infections

Austin Area Society of Health-System Pharmacists

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- The speaker has no actual or potential conflicts of interest in relation to this presentation.
- Presentation will include discussion of off-label uses of medications.

Pharmacist Learning Objectives

At the completion of this activity, the participant will be able to:

- *List the most common pathogens* that result in development of community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses
- *Differentiate signs/symptoms and diagnostic criteria* of community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses
- *Select appropriate empiric and definitive therapy* for a patient with community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses

Technician Learning Objectives

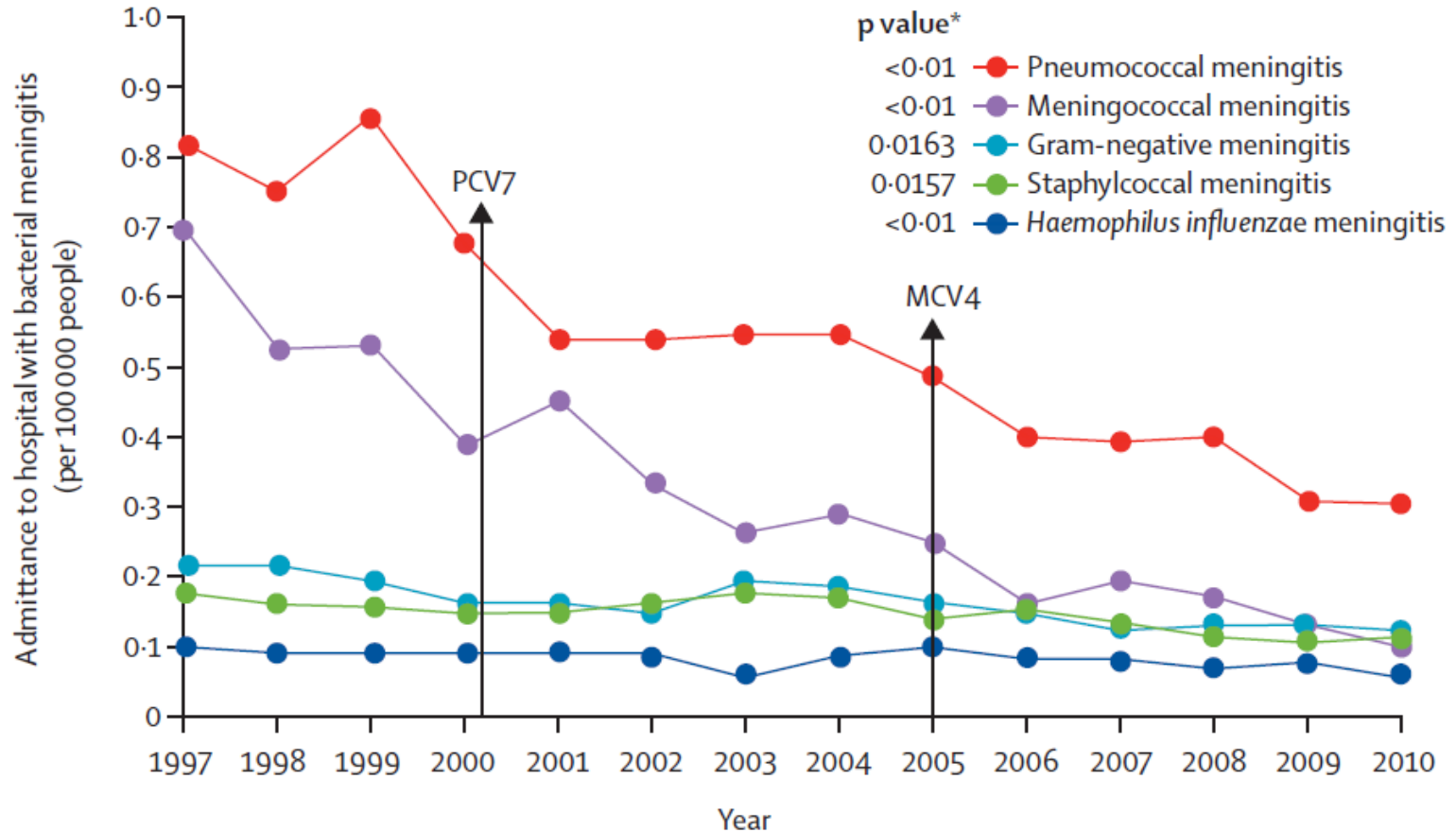
At the completion of this activity, the participant will be able to:

- *State the most common pathogens* that result in development of community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses
- *Classify the signs/symptoms* of community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses
- *Identify appropriate antimicrobial selections* for a patient with community-acquired meningitis, healthcare-associated meningitis and ventriculitis, and brain abscesses

Abbreviations

- AUC, area under the curve
- CNS, central nervous system
- CSF, cerebrospinal fluid
- KG, kilogram
- MIC, minimum inhibitory concentration
- MG, milligram
- MRSA, methicillin-resistant *S. aureus*
- PCR, polymerase chain reaction
- WBC, white blood cell

Meningitis Trends (1997-2010)¹



Community-Acquired Meningitis²

- Incidence of infection:
(number of cases per 100,000 persons/year)
 - Neonates, 300 cases
 - Older infants & children, 2-3 cases
 - School age children & adulthood, 1 case
- Pathogenesis: Colonization of the nasopharynx or skin

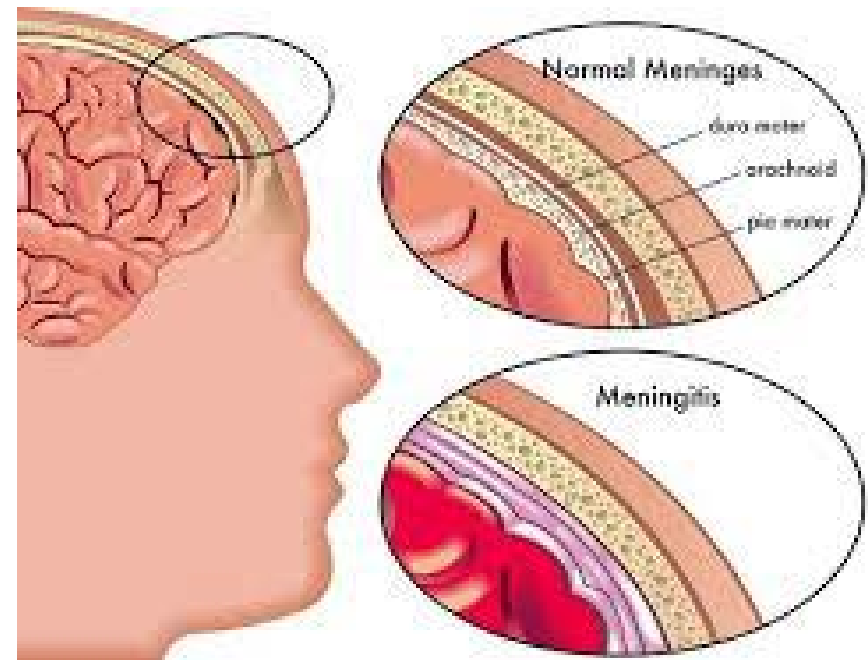
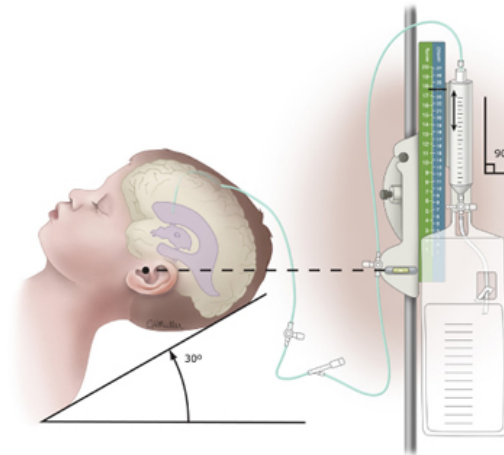
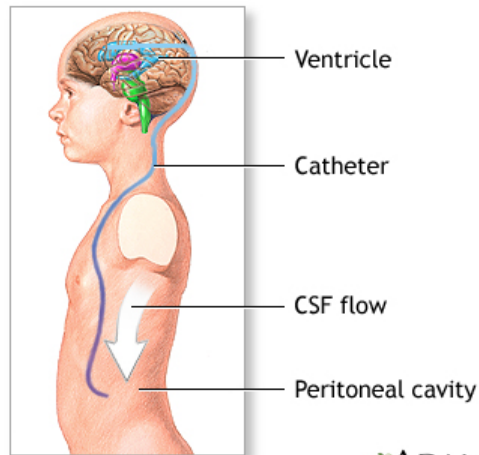
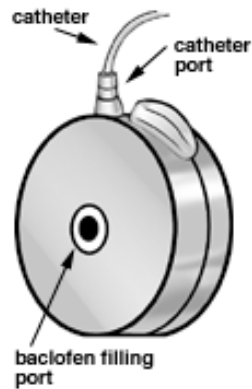


Image: <https://iytmed.com/symptoms-of-meningitis/>

Healthcare-Associated Ventriculitis and Meningitis



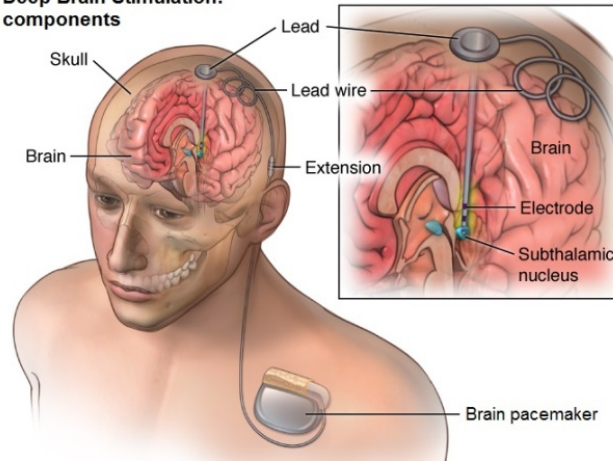
ADAM.



intrathecal baclofen pump system



Deep Brain Stimulation: components



Images:

<http://keckmedicine.adam.com/content.aspx?productId=117&pid=1&gid=003019>

http://www.lhsc.on.ca/Health_Professionals/CCTC/procedures/ICP_Fluid_Pressure_Monitoring.htm

<http://www.clevelandclinic.org/health/health-info/docs/0300/0369.asp?index=4590>

<https://bookimed.com/clinics/procedure=deep-brain-stimulation/>

Healthcare-Associated Ventriculitis and Meningitis³

- Incidence of infection:
 - 4-17% cerebrospinal fluid shunt
 - 0-22% cerebrospinal fluid drain
 - 3.6-20% intrathecal infusion pump
 - 0.62-14.3% deep brain stimulation hardware
- Pathogenesis:
 - Direct inoculation at time of surgery or injury
 - Retrograde infection from the distal end of shunt/drain
 - Contiguous
 - Hematogenous

Brain Abscess^{4,5}

- Incidence of infection:
 - All age groups
 - Peak between ages 4 - 7 years
- Pathogenesis:
 - Contiguous
 - Hematogenous
 - Direct inoculation at time of surgery or injury
- Predisposing factors:
 - Sinusitis
 - Chronic otitis media
 - Mastoiditis
 - Cyanotic heart disease
 - Endocarditis
 - Immunocompromising condition

Patient Case: SJ

- 10 month old male presenting with fever and irritability
- Past medical history:
 - Born at 23 weeks gestation, required prolonged neonatal intensive care stay
 - Required subgaleal shunts, ventriculostomy
 - Ventricular peritoneal shunt placed ~2 weeks ago
- Physical exam: pustular lesion near the site of surgical site incision
- Up-to-date on vaccines
- Social and family history unremarkable
- No known drug allergies

General Principles: Common Pathogens

Age

Predisposing/
underlying
condition

Immunization
status

Host immunity

Exposure

Season

Community-Acquired: Common Pathogens^{2,6}

Less than 1 month

- Group B streptococcus (*Streptococcus agalactiae*), *E. coli*, *Listeria monocytogenes*, *Klebsiella/Enterobacter* spp.

1 month to 23 months

- *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, Group B streptococcus (*Streptococcus agalactiae*), *E. coli*

24 months to adulthood

- *Streptococcus pneumoniae*, *Neisseria meningitidis*

Greater than 50 years old

- *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, aerobic gram negative bacilli

Healthcare-Associated: Common Pathogens^{3,6}

Cerebrospinal Fluid Shunt or Drain

- *S. aureus*, coagulase-negative staphylococcus, *Propionibacterium acnes*, *E. coli*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Pseudomonas aeruginosa*

Penetrating Head Trauma

- *S. aureus*, coagulase-negative staphylococcus, Streptococci, *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Clostridium* spp.

Intrathecal Infusion Pump

- *S. aureus*, gram negative bacilli

Deep Brain Stimulation Hardware

- *S. aureus*, coagulase-negative staphylococcus, *Propionibacterium acnes*

Brain Abscess: Common Pathogens^{4,5}

Source	Common Sites	Common Pathogens
Sinusitis	Frontal or temporal lobe	<i>Streptococcus</i> spp., <i>Staphylococcus aureus</i> , anaerobes
Otitis, Mastoiditis	Temporal lobe, cerebellum	Anaerobes, <i>Pseudomonas</i> spp., <i>Proteus</i> spp.
Dental Infection	Frontal or temporal lobe	Anaerobes, <i>Streptococcus</i> spp.
Penetrating Injury	Area of disruption	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Clostridium</i> spp., <i>Pasteurella multocida</i>
Congenital heart disease	Middle cerebral artery distribution	<i>Streptococcus</i> spp.
Immunocompromised	Any	Any of the above, <i>Candida</i> , <i>Aspergillus</i> , <i>Nocardia</i> , <i>Listeria monocytogenes</i> , <i>Toxoplasma gondii</i>

Streptococcus milleri group: *S. constellatus*, *S. intermedius*, *S. anginosus*

Anaerobes: *Bacteroides*, *Prevotella*, *Peptostreptococcus* spp.

General Principles: Signs and Symptoms

Past medical
and surgical
history

Age

Suspected
pathogen

Location of
infection

Duration of
disease

Signs and Symptoms³⁻⁸

Community-Acquired

Stiff neck
Irritability
Photophobia
Bulging fontanelle
Poor feeding
Fever/Hypothermia
Tachycardia
Myalgia
Back pain
Petechiae/purpura

Healthcare-Associated

Abdominal pain
Erythema, purulent drainage,
swelling at incision site
Fever with no clear source
Glomerulonephritis
Pleuritis
Meningismus

Headache
Nausea
Lethargy
Mental status changes

Fever
Vomiting
Papilledema
Focal neurologic deficit,
depends on abscess location
Seizures

Brain Abscess

Diagnostics: Obtain Cerebrospinal Fluid³⁻⁸

- Opening pressure
- Color
- Cell count
- Glucose
- Protein
- Gram stain
 - Gram (+) diplococci = *S. pneumoniae*
 - Gram (-) diplococci = *N. meningitidis*
 - Gram (-) coccobacilli = *H. influenzae*
 - Gram (+) cocci = *S. aureus*
 - Gram (+) rods/coccobacilli = *L. monocytogenes*
- Culture
- Contraindications to lumbar puncture:
 - Increased intracranial pressure
 - Shock
 - Convulsions
 - Coagulation abnormalities
 - Extensive/spreading purpura
 - Respiratory insufficiency

Cerebrospinal Fluid Findings³⁻⁸

	Pressure (mm H ₂ O)	Leukocytes/mm ³	Protein (mg/dL)	Glucose (mg/dL)
Community-Acquired	Usually elevated	Several hundred to >10,000 Usually 1000-5000	Elevated Usually 100-500	Low <40 in more than half the cases
Healthcare-Associated	Normal, elevated	Normal, elevated, or increasing > 7500 highly suggestive of infection	Normal, elevated, or increasing	Normal, decreased, or declining <10 highly suggestive of infection
Brain Abscess	Elevated, normal ~20%	< 500	Elevated	Normal, <40 in $\frac{1}{3}$ of cases

Other Diagnostic Tests³⁻⁸

- Complete blood count
- Serum glucose
- Blood culture
- Polymerase chain reaction (CSF)
 - Broad range 16S rRNA
 - Real-time
- Imaging
 - Computed tomography
 - Magnetic resonance imaging
- Procalcitonin (serum, CSF)
- Lactate (CSF)
- C-reactive protein
- Erythrocyte sedimentation rate
- Latex agglutination

Antibiotic “Pretreatment”^{3,6-8}

- Cell count, glucose, and protein unchanged clinically
- CSF culture
 - Antibiotic treatment > 24 hours greatest impact
 - *N. meningitidis*, sterilization in 2 hours
 - *S. pneumoniae*, sterilization in 4 hours
- Oral antibiotics less impact on *H. influenzae* versus *S. pneumoniae* or *N. meningitidis*
- PCR may be helpful for pathogen identification
- Negative CSF gram stain and culture does not exclude infection

Back to SJ

- Vital signs
 - Temperature 102.7°F
 - Pulse 183
 - Respiratory rate 32
 - Blood pressure 122/94 mmHg
 - 99% O₂ saturation on room air
 - Complete blood count
 - WBC 15.4 x 10³/uL (65% neutrophils)
 - Hemoglobin 11.4 g/dL
 - Hematocrit 32.5%
 - Platelets 471 x 10³/uL
 - Erythrocyte sedimentation rate 5 mm/hr
 - C-reactive protein < 0.5 mg/dL
 - Serum glucose 125 mg/dL
- CSF
 - Slightly cloudy, colorless
 - WBC 361 cells/uL
 - Red blood cell 3/uL
 - Neutrophils 58/uL
 - Lymphocytes 12/uL
 - Glucose 33 mg/dL
 - Protein 149 mg/dL
 - CSF gram stain
 - Abundant white blood cells
 - Scant gram positive cocci
 - CSF culture pending

What antibiotics should SJ receive for empiric therapy?

- A. Ceftriaxone
- B. Ceftriaxone and vancomycin
- C. Cefepime
- D. Cefepime and vancomycin
- E. Meropenem

What antibiotics should SJ receive if previously healthy with no significant past medical history?

- A. Ceftriaxone
- B. Ceftriaxone and vancomycin
- C. Cefepime
- D. Cefepime and vancomycin
- E. Meropenem

What antibiotics should SJ receive if 10 years old? 40 years old? 80 years old?

- A. Ceftriaxone
- B. Ceftriaxone and vancomycin
- C. Cefepime
- D. Cefepime and vancomycin
- E. Ceftriaxone and vancomycin and ampicillin

General Antibiotic Principles^{3,6}

- Must penetrate the CNS
- Must attain adequate CSF concentrations
- Must have rapid bactericidal activity against the infecting pathogen
- Ideally active in purulent CSF
- Consider local susceptibility patterns
- Consider patient's previous pathogens, if applicable

Empiric Treatment³⁻⁶

Community-Acquired

Less than 1 month old

Ampicillin PLUS Cefotaxime
Ampicillin PLUS Gentamicin

Greater than and equal to 1 month old

Ceftriaxone or Cefotaxime
PLUS Vancomycin

Greater than 50 years old

Ceftriaxone or Cefotaxime
PLUS Vancomycin PLUS Ampicillin

Healthcare-Associated

Anti-pseudomonal B-lactam PLUS Vancomycin
(cefepime, meropenem, ceftazidime)

Brain Abscess

Ceftriaxone PLUS Metronidazole ± Vancomycin
Cefepime PLUS Metronidazole PLUS Vancomycin

Should SJ receive adjunctive dexamethasone?

- A. Yes
- B. No

Adjunctive Dexamethasone for Community-Acquired Meningitis⁶

- Neonates: insufficient data to recommend
- Infants and children:
 - *S. pneumoniae*, insufficient data to recommend routinely
 - *H. influenzae*
 - Significantly reduces hearing loss associated with meningitis
 - Use may be considered after weighing risks versus benefits
- Adults: significantly lower rate of adverse outcomes and mortality with *S. pneumoniae*
- Dexamethasone 0.15 mg/kg intravenously every 6 hours for 2-4 days
- Start 10-20 minutes before antibiotics or with antibiotics (no more than 1 hour after antibiotics)

Back to SJ

- SJ was started on cefepime and vancomycin
- CSF culture updated
 - Methicillin resistant *S. aureus*
 - Vancomycin MIC 1 ug/mL

What antibiotics should SJ receive for definitive therapy?

- A. Vancomycin
- B. Linezolid
- C. Daptomycin
- D. Trimethoprim/sulfamethoxazole
- E. Vancomycin and rifampin

Definitive Treatment: Gram Positive^{3,6}

Pathogen	Antimicrobial Therapy
Methicillin sensitive <i>Staphylococci</i>	nafcillin or oxacillin
Methicillin resistant <i>Staphylococci</i>	vancomycin
Group B streptococcus (<i>Streptococcus agalactiae</i>)	ampicillin or penicillin G
<i>Propionibacterium acnes</i>	penicillin G
<i>Clostridium spp.</i>	penicillin G
<i>Listeria monocytogenes</i>	ampicillin or penicillin G

What antibiotics should SJ receive for definitive therapy if identified as *S. pneumoniae*?

- A. Penicillin
- B. Ceftriaxone
- C. Vancomycin
- D. Ceftriaxone and vancomycin
- E. Vancomycin and rifampin

What if SJ had *Streptococcus pneumoniae*?

Antimicrobial	Interpretation	MIC
Penicillin (non-meningitis)	S	0.12
Penicillin (meningitis)	I	0.12
Ceftriaxone (non-meningitis)	S	0.25
Ceftriaxone (meningitis)	I	1
Vancomycin	S	1

Streptococcus pneumoniae^{3,6,9}

Susceptibilities	Antimicrobial Therapy
Penicillin MIC \leq 0.06 ug/mL	penicillin G or ampicillin
Penicillin MIC \geq 0.12 ug/mL Cefotaxime/ceftriaxone MIC $<$ 1.0 ug/mL	ceftriaxone or cefotaxime
Penicillin MIC \geq 0.12 ug/mL Cefotaxime/ceftriaxone MIC \geq 1.0 ug/mL	vancomycin PLUS ceftriaxone or cefotaxime

Definitive Therapy: Gram Negative^{3,6}

Pathogen	Antimicrobial Therapy
<i>H. influenzae</i> (beta lactamase negative)	ampicillin or penicillin
<i>H. influenzae</i> (beta lactamase positive)	ceftriaxone or cefotaxime
<i>N. meningitidis</i> penicillin MIC < 0.1 ug/mL	penicillin or ampicillin
<i>N. meningitidis</i> penicillin MIC 0.1-1.0 ug/mL	ceftriaxone or cefotaxime
<i>E. coli, Klebsiella spp.</i>	ceftriaxone or cefotaxime
<i>Pseudomonas aeruginosa</i>	cefepime, ceftazidime, meropenem
Extended spectrum b-lactamase Enterobacteriaceae	meropenem

Definitive Therapy: Other Considerations³

- May consider rifampin with antistaphylococcal antibiotics especially if foreign material present
- May consider linezolid, daptomycin, trimethoprim/sulfamethoxazole if MRSA vancomycin MIC ≥ 1 ug/mL
- May consider aztreonam or fluoroquinolone if anaphylaxis to beta-lactam antimicrobial agents and meropenem is contraindicated for gram negative pathogens

Dosing^{3,10,11}

Antibiotic	Dose	Dosing Interval	CSF Penetration†
Ampicillin	75-100 mg/kg 2 grams	Every 6 hours Every 4 hours	13-35% (inflamed)
Cefepime	50 mg/kg 2 grams	Every 8 hours	0.103 (inflamed), 0.078 (non-inflamed)
Cefotaxime	75-100 mg/kg 2 grams	Every 6-8 hours Every 4-6 hours	0.17 (inflamed), 0.12 (non-inflamed)
Ceftazidime	67 mg/kg 2 grams	Every 8 hours	18-45% (inflamed), 0.057 (non-inflamed)
Ceftriaxone	50-100 mg/kg 2 grams	Every 12-24 hours Every 12 hours	1.5-16% (inflamed), 0.007 (non-inflamed)
Metronidazole	10-15 mg/kg 500-1000 mg	Every 8 hours Every 8-12 hours	0.87 (inflamed)
Meropenem	40 mg/kg 2 grams	Every 8 hours	0.39 (inflamed), 0.21-0.25 (non-inflamed)
Nafcillin Oxacillin	50 mg/kg 2 grams	Every 6 hours Every 4 hours	nafcillin: good oxacillin 0.02 (non-inflamed), 0.2 (inflamed)
Penicillin	50,000-100,000 units/kg 4 million units	Every 4-6 hours Every 4 hours	5-10% (inflamed)
Vancomycin	15 mg/kg 15-20 mg/kg (Max 2 g)	Every 6 hours Every 8-12 hours	0.30 (inflamed), 0.14-0.18 (non-inflamed)

†CSF penetration (presented as % of serum) or ratio of AUC_{CSF}/AUC_{serum} (presented as decimal)

Follow-Up Diagnostics³⁻⁶

- Healthcare-associated
 - Removal of infected device \pm external ventricular drain, if applicable
 - Daily CSF sampling: WBC, glucose, protein, gram stain, culture
- Community-acquired
 - Repeat lumbar puncture
 - Lack of clinical response after 48 hours
 - Gram negative meningitis in neonate
 - *S. pneumoniae* meningitis with penicillin and cephalosporin resistance
 - Patient received dexamethasone
- Brain abscess
 - Surgical intervention preferred however medical management may be considered when,
 - Symptoms less than 1 week
 - Abscesses 2 – 4 cm
 - Organism identified with another source
 - Multiple abscesses or in critical or high risk anatomic sites
 - Follow-up imaging every 1 – 2 weeks and near the end of therapy
 - Corticosteroids reserved for cases of severe or progressively increased intracranial pressure or neurological deterioration
 - Consider prophylactic antiepileptic medication during treatment and up to 3 months after treatment

Intraventricular Antibiotic Therapy³

- Insufficient evidence to recommend routine use
- Consider if lack of improvement with systemic therapy
- Administration
 - Use preservative free formulations
 - Instill and clamp drain for 15-60 minutes
- Dosing
 - CSF antimicrobial concentrations 10-20 times the MIC of the causative microorganism
 - Ventricular size/volume
 - Daily output from the ventricular drain

Intraventricular Antibiotic Dosing³

- Daily intraventricular dose
 - Gentamicin 1-8 mg (4-8 mg adults, 1-2 mg children)
 - Tobramycin 5-20 mg
 - Vancomycin 5-20 mg
 - Decrease doses ~50-60% or more in neonates and infants
- Ventricle size/volume
 - Increase dosing if enlarged ventricles > normal size > slit ventricles
- Frequency of administration based on external ventricular drain output over 24 hours
 - <50 mL: every 3rd day
 - 50-100 mL: every 2nd day
 - 100-150 mL: once daily
 - 150-200 mL: increase dose and give once daily
 - 200-250 mL: increase dose and give once daily

How long should SJ receive antibiotics for definitive therapy for methicillin resistant *S. aureus*?

- A. 7 days
- B. 14 days
- C. 21 days
- D. 28 days
- E. Greater than 28 days

Duration of Therapy: Community-Acquired⁶

Pathogen	Duration of therapy
<i>S. pneumoniae</i>	10-14 days
<i>N. meningitidis</i>	7 days
<i>H. influenzae</i>	7 days
Group B streptococcus (<i>S. agalactiae</i>)	14-21 days
Gram negative bacilli	21 days
<i>Listeria monocytogenes</i>	≥ 21 days

Duration of Therapy: Healthcare-Associated³

SHUNT		
Pathogen	Duration of Therapy	Timing for Re-implantation
<i>S. aureus</i>	10-14 days	Negative CSF cultures for 10 days
Coagulase-negative staphylococcus Propionibacterium acnes No to minimal CSF pleocytosis Normal CSF glucose Few signs or symptoms	10 days	Negative CSF cultures for 48 hours
Coagulase-negative staphylococcus Propionibacterium acnes Significant CSF pleocytosis Decreased CSF glucose Clinical signs or symptoms	10-14 days	Negative CSF cultures for 7-10 days
Gram negative bacilli	10-14 days	Negative CSF cultures for 10 days

Duration of Therapy: Brain Abscess^{4,5}

- Most patients will receive 6-8 weeks of IV antibiotics
- If surgical drainage then duration of therapy may be shortened to 3-4 weeks
- Consider transitioning to oral antimicrobial therapy after completion of intravenous therapy (i.e. linezolid, rifampin, metronidazole, and trimethoprim/sulfamethoxazole)

Thank You!

QUESTIONS?

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Credit Code: qW2L

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