

Meningitis & CNS Infections

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 IDSA Meningitis Guidelines

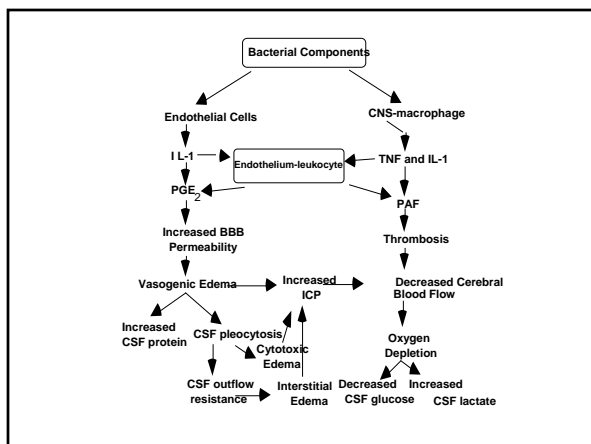
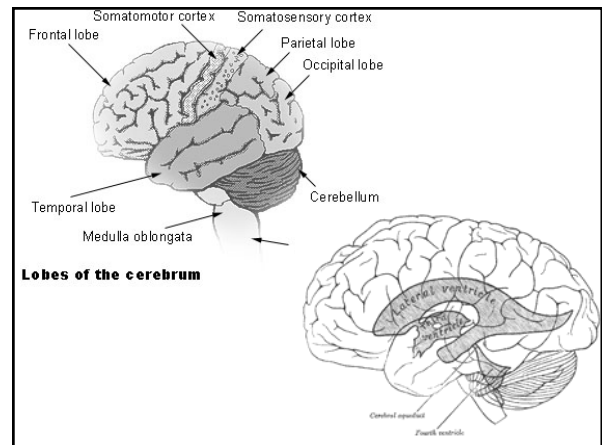
Objectives

Mitropoulos, I et al Central Nervous System Infections. In: Pharmacotherapy: A Pathophysiologic Approach, 7th edition. Editors: JT DiPiro, McGraw-Hill.

- ♦ Identify basic components of CNS anatomy
- ♦ Identify pathogens responsible causing CNS infection
- ♦ Be able to identify abnormalities in CSF chemistry & cytology associated with meningitis
- ♦ Be able to identify specific components of a physical exam that would suggest meningitis
- ♦ Identify appropriate empiric antibiotic regimens for bacterial meningitis

CNS Infections

- ♦ **Meningitis**
 - Infection of the subarachnoid space with meningeal involvement
 - Mechanical barriers intact vs. traumatic alteration
- ♦ **Encephalitis**
 - Inflammation of brain
- ♦ **Meningoencephalitis**
 - Inflammation of brain with meningeal involvement
- ♦ **Shunt or Foreign Device Infections**
 - Infected VP or VA shunt
 - CSF pressure monitoring devices
- ♦ **Brain Abscess**
- ♦ Pathogens may be bacterial, TB, viral, fungal, or parasitic



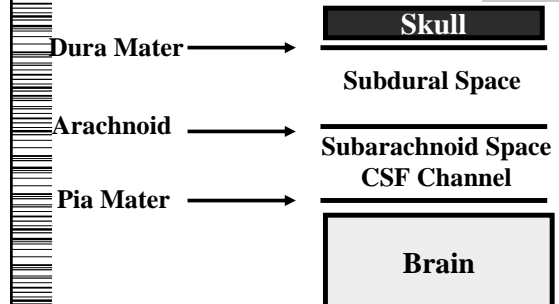
Morbidity & Mortality

- ♦ Seizure Disorder
- ♦ Blindness
- ♦ Deafness
- ♦ Learning Disabilities
- ♦ Death

Meningitis

- ♦ If a physician were attempting to do a “spinal tap” to obtain CSF for analysis, where would the needle likely be inserted and what would be the anatomical target?

Meninges



Meningitis

- ♦ What would be the typical profile of CSF if the meningitis were caused by bacteria in terms of WBC, glucose, & protein?

Typical Patient with Bacterial Meningitis

- CSF cloudy
- Opening CSF pressure 200-500 mm (water)
- WBC 1,000-5,000/mm³ (>80% Neutrophils)
- Protein 100-500 mg/dL
- Glucose < 40 mg/dL
- CSF glucose/Blood glucose ratio ≤ 0.4
- Gram Stain positive 60-90%
- CSF culture positive 70-85%

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Clinical Presentation and Diagnosis

Abnormal CSF-findings by type of meningitis

Type	WBC/mm ³	Differential	Protein (mg/dL)	Glucose
Normal	< 5	>90% mono's	< 50	50-66% serum
Bact	400-100,000	>90% PMN's	80-500	< 50% serum
Viral	5-500	>50% lymphs+	30-150	NML/low
Fungal	40-400	>50% lymphs	40-150	NML/low
T.B.	100-1,000	>80% lymphs+	40-150	NML/low

+initially CSF WBC may be PMN's but will convert to Lymph's over time

Meningitis

- ♦ What is/are the likely pathogen/s?
 - 4 day old child
 - 8 mo old child
 - 30 yr old adult
 - 85 yr old adult
 - 25 yr old adult MVA victim in ICU

Meningitis Bacterial Pathogens

- ♦ Neonatal
 - Children \leq 1 month of age
 - Pathogens acquired from birth canal
 - *E. coli*
 - Group B Streptococci (*S. agalactiae*)

Meningitis Bacterial Pathogens

- ♦ Mechanical Barriers Intact
 - *S. pneumoniae* (pneumococci)
 - *N. meningitidis* (meningococci, Groups A,B,C,Y, & W135)
 - *H. influenzae* (type B or Hib)
 - Immunizations may also affect likely pathogen
 - Special situations *B. anthracis*
- ♦ Traumatic alteration or other risk factors
 - *S. aureus*
 - *E. coli* or *P. aeruginosa*
 - May depend on circumstances

Bacterial Meningitis: Most Likely and Empiric Therapy by Age Group

Age Commonly Affected	Most Likely Organisms	Empiric Therapy	Risk Factors for All Age Groups
Newborn-1month	Gram-negative enteric <i>L. monocytogenes</i> Group B streptococcus	Ampicillin + Cefotaxime or Ceftriaxone or Aminoglycoside	Respiratory tract infection Otitis media Mastoiditis Head Trauma Alcoholism High-dose steroids Splnectomy Sickle cell disease Immunoglobulin deficiency Immunosuppression
1 month - 4 years	<i>H. influenzae</i> <i>N. meningitidis</i> <i>S. pneumoniae</i>	Cefotaxime or Ceftriaxone and Vancomycin	
5 - 29 years	<i>N. meningitidis</i> <i>S. pneumoniae</i> <i>H. influenzae</i>	Cefotaxime or Ceftriaxone and Vancomycin	
30 - 60 years	<i>S. pneumoniae</i> <i>N. meningitidis</i>	Cefotaxime or Ceftriaxone and Vancomycin	
> 60 years	<i>S. pneumoniae</i> Gram-negative enterics <i>L. monocytogenes</i>	Ampicillin + Cefotaxime or Ceftriaxone or Aminoglycoside and Vancomycin	

Listeria monocytogenes

- ♦ Uncommon CNS pathogen in adults
 - More commonly seen in the young, old, alcoholics, & immunocompromised
- ♦ Gram positive coccobacilli but can be confused as gram positive diplococci or diphtheroid
- ♦ At risk patients should have empiric coverage for this pathogen
- ♦ Probably best treated with Penicillin G or Ampicillin plus gentamicin
 - TMP/SMX maybe an alternative

Meningitis

- ♦ Most empiric regimens suggest a 3rd generation cephalosporin such as ceftriaxone plus vancomycin.
 - Is there overlap on the gram positive coverage?
 - Is there any concerning gaps in coverage?

FDA Pneumonia Breakpoints for *S. pneumoniae* (2008)

- Sensitive
 - PCN MIC \leq 2 (Previously 0.06 mg/L)
- Non-susceptible
 - PCN MIC = 4 (Previously 0.12 to 1.0 mg/L)
- Resistant
 - PCN MIC \geq 8 mg/L (Previously \geq 2 mg/L)
- Meningitis breakpoint for penicillin sensitive remains at \leq 0.06 mg/L
 - Mechanism of resistance is alteration of penicillin binding proteins not beta-lactamase production

Antimicrobial Agents of First Choice and Alternative Choice in Treatment of Meningitis Caused by Gram-positive Microorganisms		
Organism	Antibiotic of First Choice	Alternative Antibiotics
Streptococcus pneumoniae		
Penicillin susceptible	Penicillin G 200,000–300,000 units/kg/day q4h IV max: 4 million units q4h IV	Cefotaxime 200 mg/kg/day q4-6h IV max 2 g q6h Ceftriaxone 100 mg/kg/day q24 h IV max: adults 2 g q12h Chloramphenicol* 100 mg/kg/day q6h max 1.5 g q6h
Penicillin resistant	Cefotaxime or Ceftriaxone and Vancomycin* 30-40 mg/kg/day IV (60 mg/kg/day IV q6h)	Cefepime 50 mg/kg/dose q12h* max: adult 2g q6h IV Or Meropenem 40mg/kg q6h IV max: adults 1 g q6h IV with Vancomycin* Linezolid 600 mg q12h IV
Group B streptococcus	Penicillin + gentamicin*	Ampicillin + gentamicin* Cefotaxime Ceftriaxone Chloramphenicol*
Staphylococcus aureus		
Penicillin resistant	Nafcillin 200 mg/kg/day q4h IV max: 2g q4h IV	Vancomycin*
Methicillin resistant	Vancomycin*	Linezolid
Staphylococcus epidermidis		
Penicillin resistant	Nafcillin	Vancomycin*
Methicillin resistant	Vancomycin*	Linezolid
Listeria monocytogenes	Ampicillin 220–400 mg/kg/day, q6h IV or Penicillin G max: 2 gq4h IV plus gentamicin*	Trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day, q6h
Bacillus anthracis	A consensus regarding recommended agents for the treatment of CNS infections caused by anthrax, or other biological warfare agents, has not been reached. Optimal treatment must be tailored to the particular pathogen and/or genetic variants of the pathogen.	

Meningitis

- ◆ You have a 35 yr old male patient with documented *S. pneumoniae* meningitis who was initially treated last evening with ceftriaxone and vancomycin. The attending asks whether he received dexamethasone?
 - What is the value if any of using dexamethasone?
 - If given how should dexamethasone be used?
 - Are there any potential drawbacks in using dexamethasone?

Dexamethasone

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- ◆ Concern is that steroids will reduce inflammation and ultimately antibiotic penetration
 - Vancomycin
- ◆ Generally recommended for children & adults with proven or suspected *S. pneumoniae* or *H. influenzae* meningitis
- ◆ Administer steroid 10-20 minutes prior to (or time of) starting antibiotics
 - Dexamethasone intravenously 0.15 mg/Kg Q6H for two or four days

Meningitis

- ◆ You learn from next door neighbor that your 5 year old's best friend and playmate was diagnosed with meningitis. Is there anything you need to be concerned with?

Pathogenesis

- ◆ Most common cause is hematogenous spread
 - Nasal colonization (Hib & *N. meningitidis*)
 - Close contacts of patient need prophylactic antibiotic
 - Organisms introduced to systemic circulation
 - Bacteria seeded into meninges via bloodstream
- ◆ Contiguous spread
 - Parameningeal infection (ears, sinuses, etc) seed pathogens to meninges
- ◆ Traumatic
 - Direct mechanical seeding of meninges

Antibiotic Prophylaxis

- ◆ *H. influenzae*
 - Rifampin
 - Child 20 mg/Kg up to 600mg Qday X 4 days
 - Adult 600mg Qday X 4 days
 - Vaccinate if appropriate
- ◆ *N. meningitidis*
 - Ciprofloxacin
 - Rifampin
 - Child (>1 month) 10 mg/Kg up to 600mg Q12H X 2 days
 - Adult 600mg Q12H X 2 days

Meningitis

- ♦ Your son or daughter is about to leave for college and their freshman year living in the dorm.
 - Are there any meningitis issues that should be addressed apriori?

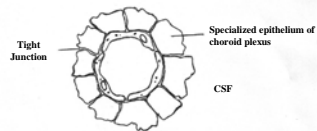
Bacterial Meningitis & Vaccination

- ♦ Prior to pediatric conjugate vaccines, *H. influenzae* type B (Hib) & *S. pneumoniae* were common cause of meningitis
 - Today *H. influenzae* in children < 4 yrs rare in USA
 - Prior to immunization, most common pathogen for that age group
 - Invasive *S. pneumoniae* disease virtually eliminated among children vaccinated with Prevnar
 - Prevnar 13 Phase 3 (2008)
 - Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
 - Group B not included
 - Wyeth has a group B vaccine in phase II (2008)

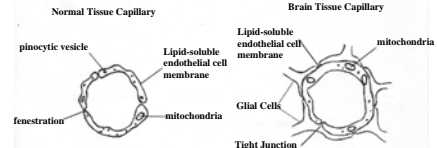
Meningitis

- ♦ Your attending is concerned about antibiotic penetration into CSF in a patient with *S. pneumoniae* meningitis being treated with ceftriaxone. Should a direct route of administration be used in this situation?

Capillary of Choroid Plexus (BCSFB)



Blood Brain Barrier (BBB)



Intraventricular and Intrathecal Antibiotic Dosage Recommendation

Antibiotic	Dose (mg)	Expected CSF conc (mg/L)
Ampicillin	10-50	60-300
Methicillin	25-100	160-600
Nafcillin	75	500
Cephalothin	25-100	160-600
Chloramphenicol	25-100	160-600
Gentamicin	1-10	6-60
Quinupristin/dalfopristin	1-2	7-13
Tobramycin	1-10	6-60
Vancomycin	5	30
Amphotericin B	0.05-0.25 mg/d to 0.05-1 mg 1-3 times weekly	--

CSF

- ♦ CSF travels in one direction through the ventricles and into the spinal column
 - Never communicates again with the point of origin
 - CSF cleared by arachnoid villi & venous plexus in spinal column
 - Creates problem for direct antibiotic placement
 - Intraventricular- drug injected into one of the lateral ventricle
 - Intracisternal- drug injected into the cisternal space at base of the skull
 - Intrathecal- drug injected into the subarachnoid space at L4-L5

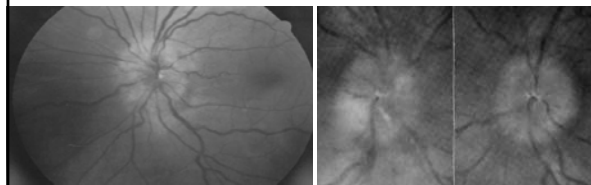
Patient Complaints

- ♦ Headache
- ♦ Nausea
- ♦ Emesis
- ♦ Fever
- ♦ Photophobia
- ♦ Seizure
- ♦ Personality Changes
- ♦ Changes in mental status
 - Irritable, delirium, drowsy, lethargy, or coma

Work up for Meningitis

- ♦ Physical Exam
 - Brudzinski's & Kernig's sign
 - Nuchal rigidity
 - Papilledema
- ♦ Lumbar puncture to obtain CSF
 - Chemistry (glucose & protein)
 - Cytology (WBC# & %PMN's)
 - Gram stain or rapid identification test (< 24hrs)
 - CIE, coagglutination, or latex agglutination
 - Limulus lysate for gram negative endotoxin
 - PCR (*N.meningitidis*, *S. pneumoniae*, *H. influenzae*, *S. agalactiae*, *L. monocytogenes* & enteroviruses)
 - Lactate (>4.2 mmol/L considered positive for bacterial meningitis)
 - Procalcitonin (> 5 micrograms/L suggestive of bacterial meningitis)
 - C-reactive proteins (CRP) (Elevated in bacterial meningitis)
 - Culture for pathogens (> 24hrs)
- ♦ Blood, Urine, & Sputum Cultures

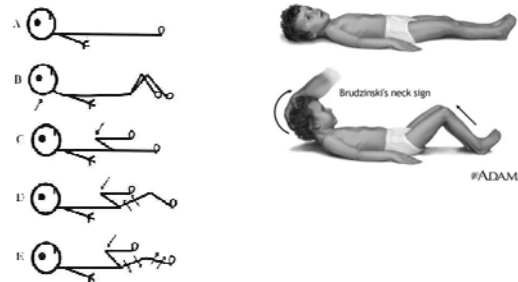
Eye Ground Exam in Meningitis



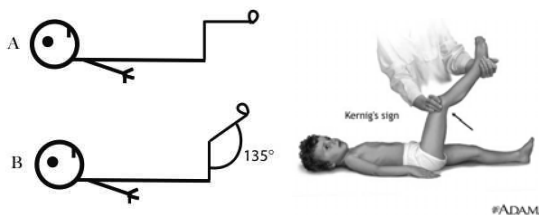
Normal

Papilledema

Brudzinski's Sign



Kernig's Sign



Antibiotic Therapy for Bacterial Meningitis

- ♦ Start antibiotics ASAP
 - Get diagnostic studies prior to antibiotic therapy
 - Start steroids prior to antibiotics
 - Pick cidal antibiotics with low molecular weight, low degree of protein binding, & are lipophilic
- ♦ Duration
 - *N. meningitidis* & *H. influenzae* 7 days
 - *S. pneumoniae* 10-14 days
 - *S. agalactiae* 14-21 days
 - Aerobic gram negatives 21 days
 - *L. monocytogenes* ≥ 21 days

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Meningitis Viral Pathogens

- ♦ Causes
 - Coxsackie, Echo, & Entero viruses cause ~85% cases
 - Mumps & Epstein Barr
 - Influenzae A & B,
 - Lymphocytic Choriomeningitis Virus & CMV
 - HSV & varicella zoster
 - Arboviruses (St Louis, La Crosse, & West Nile)
- ♦ No definitive therapy for most viral disease
 - Support patient
 - Acyclovir for HSV I & Mosquito bite prophylaxis

Brain Abscess

- ♦ Spread
 - Contiguous focus
 - Sinuses, middle ear, dental infection
 - Hematogeneous spread from primary site
- ♦ Location
 - Frontal or temporal most common
 - Parietal vs cerebellar vs occipital
 - Epidural
 - Subdural

Brain Abscess

- ♦ Microbiology
 - Anaerobes
 - Streptococci (*S. milleri*)
 - Staphylococci
 - Gram negatives uncommon
 - Fungi & parasitic infections
- ♦ Risk Factors
 - Trauma, neurosurgery, HIV, immunocompromised, sinusitis, or mastoiditis

Brain Abscess

- ♦ Patients present similar to meningitis
- ♦ Focal neurological defects occur later in the course of the disease
- ♦ Headache, fever, papilledema (avoid LP), or evidence of space lesion in CNS
- ♦ Therapy includes high dose antibiotics (6-8 wks), neurosurgery, & \pm steroids

Encephalitis

- ♦ Viruses USA
 - Eastern & Western Equine
 - St Louis
 - West Nile
 - California group
- ♦ Other world viruses
 - Venezuelan equine
 - Japanese Encephalitis
- ♦ Other viral concerns
 - HSV, mumps, measles, VZ, EB, CMV, & Rabies

Conclusions

- ♦ Great progress made with immunizations for possible meningeal pathogens
- ♦ CNS infections still have mortality of ~30%
- ♦ Rapid diagnosis and treatment imperative to optimal outcome
- ♦ Role of steroids better defined
- ♦ Much work needs to be done in diagnosing and treating viral, fungal, and parasitic disease