CNS INFECTIONS:

- Meningitis: inflammation of the membranes of the brain and spinal cord (in CSF b/w pia & arachnoid membranes)
  - CSF infants: 40-60 mL; children 60-100 mL; adults 110-160 mL
- Encephalitis: inflammation of the brain
- Meningoencephalitis: inflammation of brain accompanied by meningitis
- Brain abscess, subdural empyema, epidural abscess, ventriculo-peritoneal shunt infections

PATHOGENESIS:

- Hematogenous: systemic bacteremia or endocarditis → meningitis
- Contiguous: colonization by potential pathogens → mucosal invasion of nasopharynx (most cases)
- Direct inoculation: direct extension of bacteria across a skull fracture → subsequent leak into CSF

ETIOLOGY:

Aseptic	Fungal, TB, rickettsia, spirochetes (syphilis), protozoa	
	Viral	Enteroviruses (85%) • Seasonal (late summer to fall) • Fecal to oral route • All age groups (typically <1 year old)
		Mumps (5-10%) • Peak late winter to early spring • Parotitis; meningitis (10-30% cases); encephalitis (rare)
		Herpes Simplex
		Others (10%)
	Non-infectious	
Septic	Bacterial	80%: S. pneum, N. meningitides, H. flu
		Group B streptococcus (GBS)
		Listeria monocytogenes
Risk Factors	• URTI, otitis media, mastoiditis • Head trauma, splenectomy, sickle cell disease • Immunocompromised host; immunosuppressive therapy • Pts with hardware (shunts, etc) • Alcoholic pts	

SEQUELAE:

- 50% of patients with meningitis have persistent neurological disabilities
  - Seizures, hearing loss, focal symptoms

MORTALITY:

- Mortality rates for CNS infections decreased since pre-antibiotic era
- BUT mortality rates from meningitis remained **constant** at 5-25%, despite highly potent antibiotics
  - Eradication of bacteria is essential for improved outcome BUT is only one of the variables involved in mortality

CLINICAL FEATURES:

- Fever
- Headache
- Meningismus (nuchal rigidity)
- Altered mental status (↓ LOC, disorientation)

95% will have 2 of the 4 signs

- Photophobia, seizures, focal neurologic signs
- Petechia
- Positive Brudzinski's sign
  - In supine position, when neck is flexed, lower extremities flex
- Positive Kernig's sign:
  - With hip & knee flexed, cannot extend knee past 135° (and/or flexion opposite knee)

LABORATORY STUDIES:

- Lumbar puncture: CSF cell count, chemistries, gram stain, culture
- Blood culture
- Sputum culture/urine culture
- Peripheral CBC and electrolytes

Slide 27 – classic CSF features (b/w normal, viral, fungal/tb, bacterial)

EMPIRIC TREATMENT

Neonates	Etiology	Usually infected by bacteria found in birth canal at time of parturition	
	Risk factors	• Early rupture of membranes • Low birth weight • Immature immune system • Immature BBB	
	Organisms	• Group B streptococci • Listeria monocytogenes • E. coli • Other gram -ve	
	Treatment	**Ampicillin + [Cefotaxime *or* Gentamicin] x 14-21 days**	
Children & Young Adults	Risk factors (children)	• Inexperienced immune system • Daycare centers • URTI	
	Risk factors (adults)	• Splenectomy • Complement deficiency • Travel (sub-Saharan Africa or annual Hajj)	
	Organisms	• S. pneumoniae • N. meningitides	
	Treatment	**[Cefotaxime *or* ceftriaxone *or* meropenem] + vancomycin x 10 days**	
Adults or immuno-compromised	Population	• Adults > 50 years old • Immunocompromised: HIV, alcoholism, debilitating illness, pregnancy	
	Risk factors	• Decreased immunity	
	Organisms	• S. pneumoniae x 10-14 days therapy • Listeria m. x 21 days therapy • N. meningitides x 5-7 days therapy • Gram negative bacilli	
	Treatment	• **[Cefotaxime *or* ceftriaxone *or* meropenem] + vancomycin + ampicillin** • **Vanco + TMP/SMX (severe B-lactam allergy)**	
Open-Head Trauma, Post-Op, CSF shunt infection	Risk factors	• Barrier breakdown • Contamination from surgery or injury • Foreign indwelling device	
	Organisms	• S. aureus • S. epidermis • Gram negative bacilli	
	Treatment	**Open-head trauma, post-op**	**[Meropenem *or* Ceftazidime *or* Cefepime] + Vanco x 10-14 days**
		CSF shunt infection	**[Cefotaxime *or* ceftriaxone] + Vanco +/- rifampin x 14 days after shunt removal**
Close-Head Trauma with Skull Fracture	Risk factors	• No barrier breakdown	
	Organisms	• S. pneumonia • H. influenza • S. pyogenes	
	Treatment	**[Cefotaxime *or* Ceftriaxone] + Vancomycin**	

DEFINITIVE TREATMENT:

H. influenza	B-lactamase (-)	Ampicillin	
	B-lactamase (+)	Cefotaxime *or* ceftriaxone	
N. meningitides		Pen G *or* ampicillin	
Listeria m.		Ampicillin +/- gentamicin	
P. aeruginosa		[Cefepime *or* Ceftazidime] +/- tobramycin	
S. aureus	MSSA	Cloxacillin	
	MRSA	Vancomycin	
S. epidermis		Vancomycin +/- rifampin	
S. pneum	Sensitive	Pen MIC < 0.06 ug/mL	Pen G *or* ampicillin
	Intermediate R	Ceftriaxone MIC 0.06 – 0.12 ug/Ml	3rd gen ceph
	Resistant	Pen MIC > 0.12 ug/mL	Vancomycin +/- meropenem

ADULT DOSING:

NOTE: abx may be administered intra-ventricularly or -thecally

- Ceftriaxone 2g IV q12h
- Meropenem 2g IV q8h
- Ampicillin 2g IV q4h
- Vancomycin 15 mg/kg IV q8-12 h (aim for troughs 15-20 mg/L)
- Cefotaxime 2g IV q4-6h
- Pen G 4 MU IV q4h
- TMP 15-20 mg/kg/day (div q6-8h)

GENERAL PRINCIPLES TO TREATMENT:

- Early diagnosis is key in outcome
- Empiric therapy is required until C&S data available
  - Consider age and risk factors
- Empiric therapy is broad and aggressive
  - Combination therapy may be required based on suspected organisms
- PK factors are key
  - Natural barriers and antibiotic properties determine CSF penetration of antibiotics

CHEMOPROPHYLAXIS:

- There is a role for chemoprophylaxis to prevent the spread of **meningococcal** and **haemophilus** meningitis but NOT for pneumococcal disease
  - Eradicate pharyngeal carriage to prevent development of disease in close contacts
- Neisseria: rifampin 600 mg bid x 4 doses (i.e. 2 days)
- Hemophilus: rifampin 600 mg po daily x 4 days

VACCINES:

1. Hemophilus influenza b conjugate (Hib)
   - All children at 2,4,6 and 18 months
2. Meningococcus C conjugate (MCC)
   - Covers serotype C
   - All children at 2 and 12 months
   - Close contacts of index case
3. Conjugate vaccines
   - All children in grade 9
   - High-risk
   - Close contacts of index case
4. Menactra (MCV4-D)
   - Licensed 2005
   - A, C, Y, W-135 conjugated to diphtheria toxoid
   - Does not require reconstitution
5. Menveo (MCV4-CRM)
   - Licensed 2010
   - A,C,Y,W-135 conjugated to CRM197
   - Requires reconstitution
6. S. pneumoniae
   - Capsular polysaccharide vaccine
     - Covers 23 serotypes (88% of cases)
     - Adults 65+
     - High risk
   - Conjugate vaccine (PCV13)
     - Covers 13 serotypes
     - All children 2,4,6,12 months
     - High risk

BARRIERS TO ANTIBIOTIC PENETRATION:

- BBB = tightly joined capillary epithelial cells, drug must penetrate endothelial cells & glial cells

Factors enhancing antimicrobial penetration	Factors reducing antibiotic activity
• Small MW • Unionized at physiological pH • Lipid soluble • Large free fraction	• Low pH of fluid • High concentration of protein in fluid • High temperature of fluid

PENETRATION OF ANTIMICROBIAL AGENTS INTO THE CSF:

Therapeutic levels in CSF (w/ or w/o inflammation) • 70-90% penetration **CRISTT**	• Chloramphenicol • Rifampin • Isoniazid • Sulfonamides • Trimethoprim • Triazole antifungals (fluconazole, itraconazole)	• Ethionamide • Metronidazole • Pyrazinamide
Therapeutic levels in CSF (w/ inflammation of meninges) • 20-50% penetration	• Pen G • Piperacillin • 3rd gens cephs (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime) • Cefuroxime (exception)	• Imipenem • Vancomycin • Ampicillin • Aztreonam • Ciprofloxacin • Acyclovir
Non-therapeutic levels in CSF • ≤ 10%	• Aminoglycosides • Clindamycin • Amphotericin B	• 1st or 2nd gen cephalosporins • Ketoconazole

CORTICOSTEROIDS:

- Dexamethasone **prior** to abx has some role for specific pathogens, age, severity of presentation
  - ↓ ICP, CNS edema, fever duration, CSF lactate & protein levels; ↑ CSF glucose
  - Blocks TNF alpha and IL-1 release
- Prognosis:
  - Children ≥ 6 wks: decreases neurological complications (ataxia, sz, focal deficit) and hearing loss by 50%
  - Adults: decreases mortality & hearing loss in adults with **S. pneum** meningitis by 40%
- Dexamethasone 0.5 mg/kg IV q6h (max 10mg/dose) x 2-4 days
  - Give 20 min before abx or with first dose, BUT NOT AFTER