INFECTIOUS MENINGITIS
INFECTIONOUS MENINGITIS

• Caused by the hematogenous or direct spread of microorganisms to the subarachnoid space
  ◦ Inflammation of the pia & arachnoid mater = meningitis

RISK FACTORS

• Age
  ◦ 70% of cases of bacterial meningitis occur in children age <5years
  ◦ >80% of all cases of meningitis occur in patients age <15years

• Immunosuppression (consider possible Listeria monocytogenes & enterobacteriaceae)
  ◦ Advanced age
  ◦ Alcoholism
  ◦ Diabetes mellitus
  ◦ Hematologic malignancy
  ◦ HIV infection/ AIDS
  ◦ Malnutrition
  ◦ Medications
    – Chemotherapy
    – Chronic glucocorticoid use
    – Immunomodulating medications
  ◦ Renal dialysis

• Splenectomy or deficiency of the terminal complement components (C5–C8)
  ◦ ↑Infection risk via encapsulated bacteria:
    – Escherichia coli
    – Haemophilus Influenzae
    – Neisseria meningitides
    – Pseudomonas aeruginosa
    – Salmonella sp.
    – Streptococcus pneumoneae

• Cranial or spinal trauma, surgery, or congenital malformation
- Spina bifida cystica + myelocele or meningomyelocele →
  - ↑ Infection risk via skin organisms (diptheroids, enterobacteriaceae, Propionibacterium acnes, Staphylococcus sp.)
- Oropharyngeal trauma
  - Streptococcus pneumoneae > others

**Infection of the:**
- **Upper respiratory tract**
  - Mastoiditis
  - Otitis media
  - Sinusitis
- **Head/ neck**
  - Cellulitis
  - Orbital infection
  - Osteomyelitis
- **Dura mater**
  - Epidural abscess

**Very rarely, immersion in warm, fresh water,** such as ponds, lakes, rivers, hot springs, or inadequately/non chlorinated pools →
- Devastating protozoal meningoencephalitis via Naegleria fowleri entrance through the nasal cribriform plate, having a 98% mortality

<table>
<thead>
<tr>
<th>CLASSIFICATION/ ORGANISMS</th>
</tr>
</thead>
</table>

**Bacterial meningitis**
- **Encapsulated bacteria**
  - *Streptococcus pneumoneae*, being most common
  - *Neisseria meningitides*, Causing 80% of community acquired bacterial meningitis
  - Haemophilus Influenza, the incidence of which has markedly ↓ as a result of childhood immunization
- **Enterobacteriaceae**, accounting for 25% of all central nervous system infections in patient’s age > 65 years
  - Escherichia coli
  - Enterobacter cloacae
  - Enterococcus faecalis
  - Klebsiella pneumoneae
  - Proteus mirabilis & vulgaris
- Providencia rettgeri
- Pseudomonas aeruginosa
- Serratia marcescens
- Listeria sp.
- Staphylococcus sp.

• Fungal meningitis
  - Cryptococcus neoformans, being most common
  - Blastomyces dermatitides
  - Coccidioides immitis
  - Histoplasma capsulatum

• Mycobacterial meningitis
  - Mycobacterium tuberculosis, being either:
    - Progressive primary infection
    - Reactivation disease

• Protozoal meningitis
  - Toxoplasma gondii
  - Naegleria fowleri

• Viral meningitis
  - Enteroviruses–50%
    - Coxsackievirus
    - Echovirus
    - Poliovirus
  - Adenovirus
  - Herpes simplex virus–HSV type 2 > 1 (encephalitis type 1–95% > > 2)
  - Human immune deficiency virus–HIV
  - Mumps virus
  - Arthropod borne viruses, termed Arboviruses
    - Eastern equine encephalitis virus
    - La Cross virus
    - Western equine encephalitis virus
    - West Nile virus
    - California encephalitis virus
    - St. Louis encephalitis virus
      All being transmitted by mosquitos
Cytomegalovirus–CMV
Epstein–Barr virus–EBV
Varicella–Zoster virus–VZV

ASEPTIC MENINGITIS
• Causes for which no microorganism can be isolated using conventional staining & cultures

• Infectious
  ◦ Partially treated bacterial meningitis
  ◦ Fungal meningitis
  ◦ Mycobacterial meningitis
  ◦ Mycoplasma pneumoneae
  ◦ Protozoal meningitis
  ◦ Rickettsial meningitis
    – Coxiella sp.
    – Ehrlichia sp.
  ◦ Spirochetal meningitis
    – Borrelia burgdorferi
    – Leptospira sp.
    – Treponema pallidum
  ◦ Viral meningitis
  ◦ Parameningeal infection
    – Brain abscess
    – Epidural abscess
    – Subdural abscess
    – Septic thrombophlebitis of the dural venous sinuses

• Noninfectious
  ◦ Medications
    – Isoniazid
    – Nonsteroidal anti–inflammatory drugs–NSAIDs
    – Metronidazole
    – Penicillins
    – Sulfamethoxazole
    – Trimethoprim
  ◦ Neoplastic disease
– Carcinomatous meningitis
– Intracranial neoplasm
- Rheumatic diseases
  – Behcet’s syndrome
  – Rheumatoid arthritis
  – Sjogren’s syndrome
  – Systemic lupus erythematosus–SLE
- Other
  – Mollaret’s meningitis
  – Sarcoidosis
  – Vogt–Koyanagi–Harada syndrome

**DIAGNOSIS**

**General**
- **Inflammatory cytokines**→
  - Anorexia→
    - Cachexia
  - Chills
  - Fatigue
  - **Fever–95% †**
  - Headache
  - Malaise
  - Night sweats
  - Weakness
- **Meningeal inflammation**→
  - **Headache**
  - Opisthotonic posture: Head hyperextended w/ the body bowed forward
  - **Stiff neck = nuchal rigidity = meningismus–90%**
    – **Brudzinski’s sign–50%** (think ‘Brudzinski’s bend’): Manual head flexion in the supine position→hip & knee flexion due to pain
    – **Kernig’s sign–50%** (think ‘Kernig’s kick’): Manual knee extension in the supine position, w/ the hip being flexed→resistance due to pain
  …w/ pain being due to inflamed meningeal tension
• Bulging fontanelles in neonates/infants

†Temperature may be normal in patients w/ chronic kidney disease (esp. w/ uremia), cirrhosis, heart failure, severe debility... or those who are intravenous drug users or taking certain medications (Acetaminophen, antibiotics, glucocorticoids, nonsteroidal anti-inflammatory drugs—NSAIDs)

Neurologic
• Meningeal ± cerebral inflammation = encephalitis &/or intracranial abscess→
  - Altered mental status—80%, indicating concomitant encephalitis
    - Confusion
    - Clumsiness
    - Lethargy
    - Delirium
    - Coma
  - ↑Intracranial pressure†→
    - Altered mental status
    - Cushing reaction‡
    - Headache
    - Nausea ± vomiting
  - Focal deficits
    - Cranial nerve palsies
    - ↓Communication ability (expression &/or understanding) = aphasia
    - Hemiparesis
    - Impaired voluntary movement = ataxia
    - Visual field deficits
  - Sensitivity to light = photosensitivity→
    - Avoidance of light = photophobia
  - Seizures – 5%

Pediatrics:
• Sensorineural hearing loss, being the #1 complication in
**neonates**
- ↑Risk w/ Streptococcus pneumoneae infection

↑May be caused by communicating hydrocephalus via arachnoid villi obstruction w/ cellular debris

‡↑Intracranial pressure→
- Vascular compression→
  - ↓Cerebral blood flow→
    - Cerebral ischemia→reflex hypertension→↑cerebral arterial pressure in order to overcome intracerebral pressure→↑cerebral blood flow. If intracerebral pressure cannot be overcome by ↑↑systemic blood pressure, ischemia→↓vasomotor center sympathetic tone→hypotension→distributive shock→death

**Cutaneous**
- Herpes simplex virus mediated vesicular skin lesions

**Hematologic**
- Inflammatory cytokines→
  - Leukocytosis
  - ↑Acute phase proteins
    - ↑Erythrocyte sedimentation rate–ESR (normal: 5mm/ decade aged + ♂ ≤10mm/h or ♀ ≤20mm/h)
    - ↑C–reactive protein–CRP (normal: <2mg/ L), responding more acutely than ESR, as it rises within several hours & falls within 3 days upon partial resolution
  - ↑Fibrinogen
  - ↑Platelets→thrombocytosis

**PROCEDURES**

**Opthalmoscopy**
- Being that the dura mater of the brain extends as a sheath around the optic nerve, connecting w/ the sclera of the eye, intracranial pressure is transmitted through the optic nerve into the eye, w/ the ophthalmologic exam in a patient w/ ↑intracranial pressure possibly showing papilledema, identified via:
**Applanation tonometry**

- After the application of topical anesthetic eye drops, a handheld electronic tonometer is used to measure intraocular pressure (normal being 10–21 mmHg) by making contact w/ & determining the force required to flatten the cornea.

**Outcomes:**
- ↑Intraocular pressure indicates ↑intracranial pressure

**Limitations:**
- False positive:
  - Glaucoma
  - Medications
    - Glucocorticoids
    - Mydriatics (ex: Atropine), being medications which dilate the pupil
  - Uveitis

---

**IMAGING**

- **Brain computed tomographic–CT scan without & w/ contrast**

**Indications:**
- All patients w/ suspected central nervous system infection, for a possible mass lesion
  - Epidural abscess/ hematoma
  - Subdural abscess/ hematoma
  - Intraparenchymal abscess/ hematoma

- **If the patient has focal neurologic signs or papilledema,** promptly obtain a head computed tomographic–CT scan without & w/ contrast prior to lumbar puncture, as when fluid is removed in the presence of a tumor, the ↑intracranial pressure produced may shift the brain downward = herniation through the tentorial notch &/or foramen magnum →
  - Death. However, the generalized inflammation occurring w/ meningitis rarely has this effect
Findings suggestive of Herpes simplex virus – HSV encephalitis:
- Reactivation from latency in the trigeminal ganglion →
  - **Temporal lobe** > frontal lobe lesions (which may take several
days to appear) w/ progression to necrosis ± **hemorrhage** →
  - **blood in the cerebrospinal fluid**

**INVASIVE PROCEDURES**

- **Lumbar puncture**
  
  **Procedure:**
  
  - Performed through the **L3–L4/ L4–L5 interspace** (typically
    found via an imaginary line connecting the iliac crests) as the
    spinal cord ends at ≈L1–L2
  
  - Basic testing requires <10mL of cerebrospinal fluid, w/ more
    required for additional tests (likely safe maximum being 20mL)

  **Side effects:**
  
  - **Post–lumbar puncture headache 10–30%**
    - Cerebrospinal fluid aspiration w/ continued leak via the lumbar
      puncture dural rent →
      - ↓Cerebrospinal fluid, w/ **loss of ≥20mL** → ↓intracranial pres-
        sure → non–nervous tissue tugging → **upright postural**
        **headache**, w/ usual onset within 48hours ± tinnitus &/or
        ↓hearing. **Relieved upon recumbency**, w/ resolution occur-
        ring gradually over hours to 2 weeks
  
  **Note:** The adult cerebrospinal fluid volume is ≈150mL, w/
  production being 450mL/ 24hours (0.3mL/min)

- Cerebral venous thrombosis – rare, not being postural

**Prevention of headache:**

- Use the smallest gauge needle practical, while aligning the bevel
  parallel to the dural fibers which run longitudinally, in order to
  separate, not cut, the fibers

- The following have not been shown to be risk factors:
  - Position or hydration before, during, or after the procedure

**Treatment of headache:**

**METHYLXANTHINES**
<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caffeine</strong> (Vivarin)</td>
<td>L/?: 500mg PO q4hours prn, being absorbed within 15–45 minutes</td>
</tr>
<tr>
<td><strong>Caffeine sodium benzoate</strong></td>
<td>500mg IM/ IV q4hours prn</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Methylxanthines ➔
  - Adenosine receptor antagonism ➔
    - Cerebral vasoconstriction

- For severe &/or prolonged headaches, ask an anesthesiologist to place an **epidural blood patch**, consisting of 20mL of autologous venous blood injected into the epidural space previously punctured ➔
  - Immediate relief in 95% of patients

**Contraindications:**
- Infection involving the path of the spinal needle
  - Cellulitis
  - Epidural abscess
- Coagulopathy (INR > 1.3 &/or PTT > 35 seconds) &/or thrombocytopenia (< 50,000/μL)
- ↑Intracranial pressure due to a localized lesion
  - Abscess
  - Localized edema
  - Localized hemorrhage
  - Neoplasm
  - …which may ➔
    - **Focal neurologic deficits**

**CEREBROSPINAL FLUID ANALYSIS**

**Lab studies:**
- **Tube 1:** Protein & glucose
- **Tube 2:** Cell count & differential
- **Tube 3:** Gram stain & culture
• **Tube 4:** Other studies as clinically indicated
  - Acid fast bacillus stain–AFB stain & culture
  - Complement fixation test for:
    - Anti–Coccidiodes immitis antibodies
    - Anti–Histoplasma capsulatum antibodies
  - Fungal staining
    - India ink staining for Cryptococcus neoformans
  - Latex particle agglutination test for:
    - Cryptococcal neoformans antigen
  - Polymerase chain reaction test for:
    - Herpes simplex viral DNA
    - Varicella–zoster viral DNA
  - Venereal disease research laboratory–VDRL test for:
    - Anti–cardiolipin–cholesterol–lecithin antibodies, produced when Treponema pallidum interacts w/host tissues
  - Enzyme linked immunosorbent assay–ELISA for Anti–West Nile virus IgM antibodies

<table>
<thead>
<tr>
<th>CEREBROSPINAL FLUID CHARACTERISTICS</th>
<th>Differential findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opening CSF pressure†</strong></td>
<td>&gt;18cm H₂O</td>
</tr>
<tr>
<td>Normal: 18cm=180mmH₂O</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Inflammation: Normal†</td>
<td>Encephalitis</td>
</tr>
<tr>
<td></td>
<td>Mass lesions</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>45–100mg/dL</td>
</tr>
<tr>
<td>Normal: &lt;45mg/ dL</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Inflammation: †</td>
<td>Viral</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td></td>
<td>&gt;200mg/dL</td>
</tr>
<tr>
<td></td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>Low</td>
</tr>
<tr>
<td>Normal: &gt;50% of plasma</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Inflammation: Normal†</td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>&gt;1000 cells</td>
</tr>
<tr>
<td>Normal: ≤4 cells/ µL</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Inflammation: †</td>
<td>Viral</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
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<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td></td>
<td>&gt;50% PMN's</td>
</tr>
<tr>
<td></td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Viral</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial</td>
</tr>
<tr>
<td></td>
<td>Spirochetal</td>
</tr>
<tr>
<td></td>
<td>Aseptic</td>
</tr>
<tr>
<td></td>
<td>&gt;50% Mono's</td>
</tr>
<tr>
<td></td>
<td>Viral</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial</td>
</tr>
<tr>
<td></td>
<td>Traumatic tap</td>
</tr>
</tbody>
</table>

† Only valid in the lateral decubitus position

**PROGNOSIS**

• In hospital mortality in adults is:
• 25% for community acquired bacterial meningitis
• 35% for hospital acquired bacterial meningitis

**TREATMENT**

**If the patient lacks focal neurologic signs & papilledema:**
- After blood cultures & cerebrospinal fluid have been obtained, begin empiric intravenous treatment promptly w/ bactericidal antibiotics, as the organism must be killed by the antibiotic alone, without help from neutrophils, which, along w/ immunoglobulin & complement proteins, have great difficulty infiltrating the central nervous system

**If either focal neurologic signs or papilledema exist:**
- After blood cultures have been obtained, begin empiric intravenous treatment promptly & obtain a head computed tomographic–CT scan to rule out a mass lesion prior to performing a lumbar puncture
  - Cerebrospinal fluid yield is unlikely to be reduced if obtained within 4 hours of antibiotic administration

**Empiric intravenous antibiotics**
- The switch to PO medication should be attempted upon clinical improvement via fever resolution & clinical stabilization X 24 hours, if an acceptable PO medication is available, & the patient is able to take PO medication
- **Organism–narrowed therapy** should be initiated promptly upon stain, culture, & sensitivities results
- The following antibiotics achieve equivalent plasma levels via PO or intravenous administration in persons w/ a functioning gastrointestinal tract:
  - Chloramphenicol
  - Doxycycline
  - Minocycline
  - Most fluoroquinolones
  - Trimethoprim/ Sulfamethoxazole
Bactericidal antibiotics: Avoid combining w/ bacteriostatic antibiotics, as bactericidal antibiotics require actively multiplying bacteria

- **Cell wall synthesis inhibitors**
  - β-lactam medications:
    - Carbapenems
    - Cephalosporins
    - Monobactams
    - Penicillins
  - Vancomycin

- **DNA synthesis inhibitors**
  - Fluoroquinolones
  - Linezolid, in part
    - Bacteriostatic against Enterococcus sp. & Staphylococcus sp.
    - Bactericidal against the majority of Streptococcus sp.
  - Metronidazole
  - Rifampin
  - Quinupristin & Dalfopristin

- **Protein synthesis inhibitors**
  - Aminoglycosides

**Treatment duration:**
- Bacterial meningitis: 3 weeks
- Fungal meningitis: 6 weeks
- Encephalitis: 3 weeks
- Abscess: 6 weeks

<table>
<thead>
<tr>
<th>CEPHALOSPORINS: 3rd–4th generation, to cover Haemophilus Influenzae, Neisseria meningitides, Streptococcus pneumoniae, &amp; enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (Trade)</strong></td>
</tr>
<tr>
<td>Cefotaxime (Claforan)</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
</tr>
</tbody>
</table>

**Mechanism:**
- A β-lactam ring structure which binds to bacterial transpeptidase→
Transpeptidase function

- Bacterial cell wall peptidoglycan cross-linking → decrease in cell wall synthesis → osmotic influx of extracellular fluid → increase in intracellular hydrostatic pressure → cell rupture → cell death = bactericidal

- Bacterial autolytic enzymes → Peptidoglycan degradation

- Certain bacteria produce β-lactamase
  - Cleavage of this essential structural component of Cephalosporins & certain Penicillins (as the other β-lactam medications differ sufficiently to prevent ring cleavage)
  - Antibiotic inactivation. This process may be antagonized by the concomitant administration of β-lactamase inhibitors (Clavulanic acid = clavulanate, Sulbactam, or Tazobactam) → renewed susceptibility

### Side effects:

#### General

- **Hypersensitivity reactions ≤ 10%**
  - Anaphylaxis → 0.5%
    - Death → 0.002% (1:50,000)
  - Acute interstitial nephritis
  - Dermatitis
  - Drug fever
  - Hemolytic anemia

- Having cross-hypersensitivity to other β-lactam medications (Penicillins, Carbapenems), except Monobactams (ex: Aztreonam)

#### Gastrointestinal

- Clostridium difficile pseudomembranous colitis (esp. 3rd generation)

---

**VANCOMYCIN:** To cover β-lactam resistant Streptococcus pneumoneae

<table>
<thead>
<tr>
<th>M/♀: Dose</th>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>K/♂: 1g IV q12hours, to be administered over 1 hour</td>
<td>30–40µg/mL</td>
<td>&gt;10µg/mL</td>
</tr>
</tbody>
</table>

- Peak levels are obtained 30 minutes post dose, w/ trough levels being obtained at the end of the dosing interval (just prior to the next dose). **Trough levels** are directly related to toxicity & clinical efficacy, whereas peak levels predict neither
Mechanism:
• Direct cell wall peptidoglycan binding →
  ◦ ↓ Transpeptidase function →
  ◦ ↓ Bacterial cell wall peptidoglycan cross-linking → ↓ cell wall synthesis → osmotic influx of extracellular fluid → ↑ intracellular hydrostatic pressure → cell rupture → cell death = bactericidal

• Vancomycin resistant enterococci–VRE & staphylococci–VRS have developed

Side effects:

General
• Rapid intravenous administration (over < 1 hour) →
  ◦ Intrinsic hypersensitivity syndrome →
    – Face, neck, &/or upper thoracic angioedema, termed ‘red man syndrome’

Treatment: Discontinue the current infusion, & administer Diphenhydramine (Benadryl) 50mg PO/ IM/ IV X 1. Once resolved, the infusion may be resumed (unless accompanied by an anaphylactoid reaction) at a ↓ infusion rate

Cardiovascular
• Venous inflammation = phlebitis ± thrombus formation

Genitourinary
• Acute interstitial nephritis

Otolaryngology
• Ototoxicity

Hematology
• Thrombocytopenia

PENICILLINS: To cover Listeria sp.

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/ ♀ Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (Principen)</td>
<td>K/ P: 2g IV q4hours</td>
</tr>
</tbody>
</table>

Mechanism:
• A β-lactam ring structure which binds to bacterial transpeptidase →
  ◦ ↓ Transpeptidase function →
  ◦ ↓ Bacterial cell wall peptidoglycan cross-linking → ↓ cell wall synthesis → osmotic influx of extracellular fluid → ↑ intracellular hydrostatic pressure → cell rupture → cell death = bactericidal
• Bacterial autolytic enzymes →
  ○ Peptidoglycan degradation

• Certain bacteria produce β–lactamase →
  ○ Cleavage of this essential structural component of Cephalosporins & certain Penicillins (as the other β–lactam medications differ sufficiently to prevent ring cleavage) →
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**Side effects:**

**General**

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  ○ Anaphylaxis – 0.5% →
    – Death – 0.002% (1:50,000)
  ○ Acute interstitial nephritis
  ○ Dermatitis
  ○ Drug fever
  ○ Hemolytic anemia

... having cross–hypersensitivity to other β–lactam medications (Cephalosporins, Carbapenems), except Monobactams (ex: Aztreonam)

**Gastrointestinal**

• Clostridium difficile pseudomembranous colitis

---

**IF HYPERSENSITIVITY TO β–LACTAM MEDICATIONS**

<table>
<thead>
<tr>
<th>CHLORAMPHENICOL (Chloromycetin): To cover Neisseria meningitides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M/♀ Dose</strong></td>
</tr>
<tr>
<td>LK/♂: 15mg/kg IV q6hours</td>
</tr>
</tbody>
</table>

**Mechanism:**

• Affects the ribosomal 50S subunit →
  ○↓ Peptidyltransferase function →
    –↓ Peptide bond formation

**Side effects:**

**Hematologic**

• Irreversible, idiosyncratic, aplastic anemia 1/ 25,000
Reversible, dose related myelosuppression

**Materno-fetal**

- Gray baby syndrome in newborns

---

**VANCOMYCIN:** To cover *Streptococcus pneumoniae*

<table>
<thead>
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<th>M/ ♀ Dose</th>
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<td>30–40μg/ mL</td>
<td>&gt;10μg/ mL</td>
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</tbody>
</table>

---

**TRIMETHOPRIM–SULFAMETHOXAZOLE TMP–SMX** (*Bactrim, Septra*): To cover *Listeria sp.*

**M/ ♀ Dose**

- K/ U PO: 2 double strength–DS tab (160mg TMP/ 800mg SMX) PO q6hours IV: 5mg/ kg TMP q6hours

- **Ensure that the patient is receiving 20mg TMP/kg/24hours**

---

**Trimethoprim specific mechanism:**

- ↓Dihydrofolate reductase action→
  - ↓Tetrahydrofolate, being required as a methyl donor for the synthesis of purines & pyrimidines→
    - ↓Nucleotide synthesis

**Sulfonamide specific mechanism:**

- A P–aminobenzoic acid–PABA analogue→
  - Competitive inhibition of dihydropteroate synthetase mediated PABA conversion to dihydrofolate→
    - ↓Tetrahydrofolate, being required as a methyl donor for the synthesis of purines & pyrimidines→ ↓nucleotide synthesis

---

**Side effects:**

**Mucocutaneous**

- **Dermatitis** via maculopapular rash, urticaria >> exfoliative dermatitis, photosensitivity, Stevens–Johnson syndrome, or toxic epidermal necrolysis

**Genitourinary**

- Acute interstitial nephritis

**Neurologic**
• Aseptic meningitis

**Pulmonary**

• The sulfite component of the combination medication →
  ○ Asthma exacerbation in sensitive patients

**Hematologic**

• **Myelosuppression** →
  ○ Anemia →
    – Fatigue
  ○ Leukopenia → immunosuppression →
    – ↑ Infection & neoplasm risk
  ○ Thrombocytopenia →
    – ↑ Hemorrhage risk

**Infusion specific:**

• Being as Trimethoprim–Sulfamethoxazole does not readily dissolve in aqueous solutions, a nonpolar solvent such as propylene glycol (a colorless, odorless fluid) is required to keep the medication in solution, & can accumulate →
  ○ **Propylene glycol toxicity** →
    – Acute tubular necrosis → renal failure
    – Altered mental status
    – Anion gap metabolic acidemia
    – Dysrhythmias
    – Hemolysis
    – Hyperosmolarity
    – Seizures
  ... → ↑ plasma levels & **osmolar gap**. Being that propylene glycol is metabolized equally by the kidneys & liver, patients w/ renal or hepatic failure are @ ↑ risk

**Trimethoprim specific:**

**Genitourinary**

• Blocks distal renal tubule Na⁺/K⁺ exchange →
  ○ **Hyperkalemia**

• Competes w/ creatinine for tubular secretion →
  ○ ↑ **Creatinine**, without concomitantly ↑ blood urea nitrogen–BUN

**Hematologic**

• ↑ Homocysteine levels
### Sulfamethoxazole specific:

**General**
- Anorexia
- Drug fever via hypersensitivity syndrome

**Gastrointestinal**
- Nausea ± vomiting

**Genitourinary**
- Crystalluria→
  - Acute tubular necrosis
- Hepatitis

**Hematologic**
- Glucose–6 phosphate dehydrogenase–G6PD deficiency mediated hemolytic anemia

### Contraindications:
- Glucose–6–phosphate dehydrogenase deficiency→
  - Hemolytic anemia
- Neonates or near term ♀️s, as sulfamethoxazole competitively binds to albumin, thus displacing bilirubin→
  - ↑Kernicterus risk

---

### CSF SHUNT, RECENT HEAD TRAUMA (including neurosurgery)

**CEPHALOSPORINS: 3rd–4th generation, to cover Pseudomonas aeruginosa**

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/ ♂: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime (Ceptaz, Fortaz)</td>
<td>K/ P: 2g IV q8hours</td>
</tr>
</tbody>
</table>

**VANCOMYCIN: To cover methicillin resistant Staphylococcus aureus–MRSA**

<table>
<thead>
<tr>
<th>M/ ♀: Dose</th>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>K/ ?: 1g IV q12hours, to be administered over 1 hour</td>
<td>30–40µg/ mL</td>
<td>&gt;10µg/ mL</td>
</tr>
</tbody>
</table>

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### VIRAL MENINGITIS

**HERPES SIMPLEX VIRUS–HSV type 1 OR 2**

**ANTIVIRAL MEDICATIONS**

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/ ♀: Dose</th>
</tr>
</thead>
</table>
OTHER THERAPEUTIC MEASURES

SYSTEMIC GLUCOCORTICOID TREATMENT

- Treatment delay of ≥72 hours after antimicrobial treatment has been initiated, offers no benefit

**Indications:**
- To be given w/ or just prior to the 1st antibiotic dose in patients w/ suspected bacterial meningitis

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>L/ ?: 10mg IV q6hours X 4days</td>
</tr>
</tbody>
</table>

- Both the IV & PO routes have equal efficacy
- Being that the total duration of systemic glucocorticoid therapy is ≤2 weeks, there is no need to taper

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Relative potencies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Cortisol (physiologic†)</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone (PO)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hydrocortisone (PO, IM, IV)</td>
<td>1</td>
</tr>
<tr>
<td>Methylprednisolone (PO, IM, IA, IV)</td>
<td>5</td>
</tr>
<tr>
<td>Prednisone (PO)</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone (PO, IM, IV)</td>
<td>5</td>
</tr>
<tr>
<td>Triamcinolone (PO, IM)</td>
<td>5</td>
</tr>
<tr>
<td>Betamethasone (PO, IM, IA)</td>
<td>25</td>
</tr>
<tr>
<td>Dexamethasone (PO)</td>
<td>25</td>
</tr>
<tr>
<td>Fludrocortisone (PO)</td>
<td>125</td>
</tr>
</tbody>
</table>

†The physiologic rate of adrenal cortical cortisol production is 20–30mg/24 hours

**Mechanism:**
- Appropriate antibiotic treatment→
  - Organism death & lysis→
    - Antigenemia→↑**meningitis** within 24 hours (usually within 2 hours) after initial treatment
- Glucocorticoids→
  - ↓Meningeal inflammation→
    - ↓Intracranial pressure
    - ↓Possible mass effect

**Outcomes:**
**Morbidity** (hearing loss & other neurologic sequelae), but **NO EFFECT ON MORTALITY**

<table>
<thead>
<tr>
<th>RIFAMYCINS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications:</strong></td>
</tr>
</tbody>
</table>
| • Any regimen which includes Vancomycin, for the duration of Dexamethasone use, as Dexamethasone
  ◦ Cerebrospinal fluid Vancomycin levels, unless administered w/ Rifampin |
| **Generic (Trade)** | **M/♀: Dose** |
| **Rifampin (Rifadin, Rimactane)** | L/♀: 600mg q24hours |
| **Dose adjustment:** |
| • Body weight < 50kg: 450mg PO q24hours |

**Side effects:**

**General**
• Flu-like syndrome w/ fevers, chills, headache, bone pain, &/or dyspnea

• **Orange discoloration of body fluids**, including sweat, tears, & urine*, which stain clothing & contact lenses. Compliance can be assessed via urine evaluation for orange discoloration

**Gastrointestinal**
• **Hepatitis**, usually asymptomatic
  **Risk factors:**
  • Age ≥ 35years
  • Alcoholism
  • Postpartum state
  • Underlying liver disease

**Mucocutaneous**
• Dermatitis

**Hematologic**
• Thrombocytopenia

**Interactions:**
• The concomitant administration of Rifampin w/ either:
  ◦ **Protease inhibitors** or
  ◦ **Nonnucleoside reverse transcriptase inhibitors–NNRTIs**
  ...→↓Plasma antiretroviral medication levels, w/ concomitantly ↑Rifampin levels.
To avoid this, replace Rifampin w/ Rifabutin which has ↓ interactions w/ protease inhibitors (except Ritonavir) & nonnucleoside reverse transcriptase inhibitors–NNRTIs (except Delavirdine)

PROPHYLAXIS

PRE–EXPOSURE PROPHYLAXIS
STEPTOCOCCUS PNEUMONEAE VACCINE
Indications:
• All persons, w/ those age <2 years requiring the conjugate heptavalent pneumococcal vaccine (Prevnar, containing 13 serotypes), w/ doses & timing varying by age
• Asplenia (being best if administered prior to asplenia)
  ◦ Anatomic
  ◦ Functional
• 2 weeks prior to immunosuppressive treatment
  ◦ Chemotherapy
  ◦ Immunomodulating medications
Dose
• 0.5 mL SC/ IM X 1, w/ a booster @ 5 years
Mechanism:
• Bacterial capsular polysaccharides of 23 serotypes (Pneumovax), accounting for 75% of invasive disease (bacteremia, meningitis, pneumonia)
Side effects:
  Mucocutaneous
  • Mild local inflammation ± soreness
Outcomes:
• 70% efficacious for 10 years
  ◦ ↓ For immunosuppressed or age < 2 years

HAEMOPHILUS INFLUENZAE TYPE B VACCINE
Indications:
• Asplenia
  ◦ Anatomic
  ◦ Functional
  … being best if administered prior to asplenia
Dose
• **0.5mL IM X1**

Mechanism:
• Bacterial capsular polysaccharide conjugated to protein

Contraindications:
• Pregnancy

**NEISSERIA MENINGITIDIES VACCINE**

Indications:
• Age 11–18 years
• College students living in dormitories
• Asplenia (anatomic or functional; being best if administered prior to asplenia) or deficiency of the terminal complement components (C5–C8)
• Military personnel
• Persons traveling to, or residing in countries in which meningococcal disease is prevalent
  ▪ Sub-Saharan Africa
• Laboratory personnel routinely exposed to isolates of N. meningitides

Dose:
• **0.5mL X 1, w/ a booster @ 5 years if indicated**
  ▪ Age ≤55 years: Conjugated vaccine IM (Menveo, Menactra) X 1
  ▪ Age >55 years: Unconjugated vaccine SC (Menomune) X 1

Dose adjustment: For patients w/ HIV infection, asplenia, or deficiency of the terminal complement components, a 2nd dose is administered @ 2 months

Mechanism:
• Bacterial polysaccharides of the serotypes accounting for most infections: A, C, Y, & W–135, but not B, as it has a polysaccharide capsule w/ some antigenic similarity to human neural glycoproteins

Side effects:
• General
• Fatigue
• Fever
• Malaise
...from 6 hours–2 days post-vaccination

**Mucocutaneous**
• Mild local inflammation ± soreness &/or induration

**Outcomes:**
• > 90% efficacious

**POSTEXPOSURE PROPHYLAXIS**

**Indications:**
• Close contacts

**HAEMOPHILUS INFLUENZAE**

<table>
<thead>
<tr>
<th>RIFAMPIN</th>
<th></th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic (Trade)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin (Rifadin, Rimactane)</td>
<td>L/ ?: 600mg q24hours X 4days</td>
<td></td>
</tr>
</tbody>
</table>

**NEISSERIA MENINGITIDES**

**FLUOROQUINOLONES**

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>LK/ ?: 500mg PO X 1</td>
</tr>
<tr>
<td>Levofoxacin (Levaquin)</td>
<td>KL/ ?: 500mg PO X 1</td>
</tr>
</tbody>
</table>

**Mechanism:**
• \( \frac{1}{2} \) DNA gyrase = topoisomerase action →
  • \( \downarrow \) Bacterial DNA synthesis

**OR**

**MACROLIDES**

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>L/ P: 500mg PO X 1dose</td>
</tr>
</tbody>
</table>
Mechanism:
• Affects the ribosomal 50S subunit →
  ◦ ↓ Transfer RNA translocation

OR

CEPHALOSPORINS: 4th generation

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>KB/ P: 250mg IM X 1</td>
</tr>
</tbody>
</table>