Treatment for Bacterial Meningitis

Structure of this summary

- Treatment strategy divided by *PATIENT AGE* (neonate, 1 month-adult)
  - Neonates
  - Children/adults
  - Elderly
- Then by *EMPIRIC* (don't know bug yet) vs *DEFINITIVE* (know bug) therapy
- Within empiric, then by *OTHER FACTORS* that may predict effective treatment prior to definitive therapy, e.g.,
  - Onset time
  - Setting of infection acquisition (usually hospital- vs community-acq.)
- Pharmacology key concepts to review

Top causes of bacterial meningitis in neonates:

- Streptococcus *agalactiae* (group B strep ((GBS)), Gram-positive coccus)
- E. *coli* (Gram-negative facultative anaerobic rod)

Other causes of bacterial meningitis in neonates:

- Staphylococcus (including MRSA)
- Listeria

Empiric Therapy in neonates (varies by time of onset and setting):

- Early-onset (<72 hr): Ampicillin + aminoglycoside (e.g., gentamicin)
- Late-onset (<72 hr): Ampicillin + aminoglycoside (e.g., gentamicin) OR ampicillin + ES ceph
- Late-onset (hospital setting): Vancomycin+ aminoglycoside: hospital-acquired
- *High-yield note*: Because treatment *delay worsens outcomes*, empiric therapy is appropriate, and MUST:
  - cover both G(+) and G(-) bacteria
  - be able to cross BBB
  - remind yourself how the empiric therapies above meet these goals

Definitive Therapy in neonates (varies by bug):

- GBS: penicillin G. Preferred BECAUSE it is
  - the most narrow-spectrum
  - the most active agent in vitro
  - less detrimental to the gut microbiome (than ampicillin)
- E. *coli*: ampicillin (an ES-PCN)
  - If ampicillin-R, then ES-cephalosporin (e.g., ceftazidime, cefepime) plus aminoglycolyside (e.g., gentamicin)

Top causes of bacterial meningitis in children and adults:

S. pneumoniae (Gram-positive cocci)
N. meningitidis/meningococcus (Gram-negative diplococcus)
H. influenza-B (Gram-negative coccobacillus)

L. monocytogenes (for elderly and/or immunocompromised pt populations)

Empiric Therapy in children/adults:

- (1mo–50 y) Vancomycin+ 3rd gen cef (e.g., ceftriaxone) or 4th gen cef (cefepime)

- (>50 y) Vancomycin+ 3rd gen cef (e.g., cefotaxime, ceftazidime, cefepime) + ampicillin

Why these cefs? 1. Good CSF penetration, 2. Potent activity against meningeal pathogens

- Note: ceftazidime is LESS effective against PCN-R strains than cefepime, ceftriaxone
- Availability note: cefotaxime is only available in the US for injection, and only with Rx.

Why this combination? 1. Vanco: targets **G(+)** only; 2. Cefs: more active against **(G-)**

- *High-yield note*: Because treatment *delay worsens outcomes*, empiric therapy is appropriate, and MUST:
  - cover both G(+) and G(-) bacteria
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Why a cef + amp in >50yo? Because of the increased likelihood of Listeria infection.

- Empiric therapy targeting Listeria as well as other likely causes (e.g., S. pneumoniae). This ALSO APPLIES to immunocompromised pt of ANY AGE.

Definitive Therapy in children/adults:

- *S.pneumoniae*: Vancomycin + ceftriaxone or cefotaxime
- *N. meningitiis*: ceftriaxone or cefotaxime
- *H. influenza* B: ceftriaxone or cefotaxime (if sensitive to it, also ampicillin)

Major side effects:

- Vancomycin: **ototoxicity and nephrotoxicity.**
- Cephalosporins: similar allergic/hypersensitivity rxn with PCN
  - Note: *contraindicated* in patients who experienced *anaphylaxis* with PCN previously.

Top causes of bacterial meningitis in elderly, immunocompromised:

- *Listeria monocytogenes* (Gram-positive rod)

Empiric therapy in elderly, immunocompromised:

Vancomycin+ 3rd gen cef (e.g., cefotaxime, ceftazidime, cefepime) + ampicillin

REVIEW KEY CONCEPTS:

• **Cell wall inhibitors are bactericidal** while **most protein synthesis inhibitors are bacteriostatic**, **except for aminoglycosides** (Gram-negative active) and **streptogramins** (Gram-positive active). Remember that CSF lacks robust humoral immunity, so drug administration is aimed at achieving bactericidal concentrations- remind yourself why a bacteriostatic therapy (e.g., clindamycin, tetracycline) would be less desirable here.

Pharmacology/Med Chem Notes to Remember:

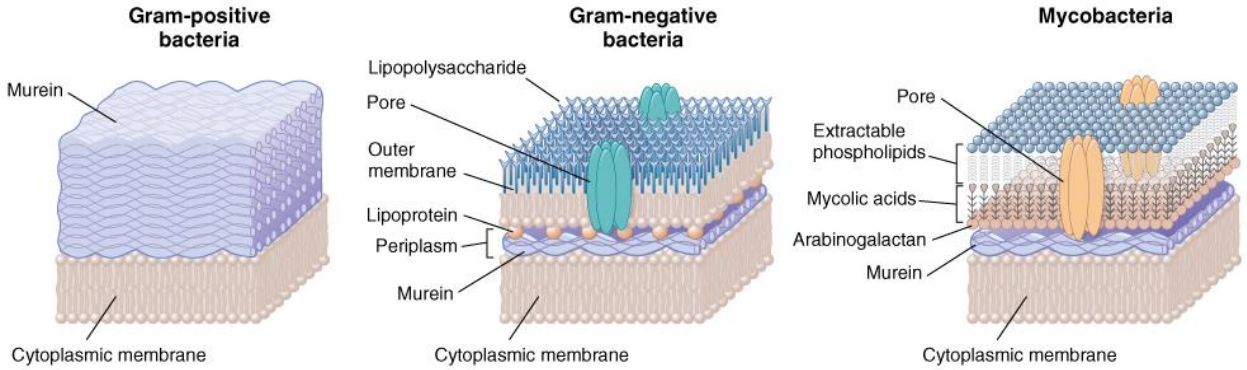
Targeting G(+) bacteria

Most drugs that are active against G(+) bacteria must diffuse across the thick bacterial cell walls. The peptidoglycan layer is not actually that great at keeping antibiotics out, but the

cytoplasmic membrane IS. The penicillin-binding proteins (PBP)s in the cytoplasmic membrane are therefore readily accessible even to the hydrophilic beta lactams.

Targeting G(-) bacteria

Drugs that are active against G(-) bacteria either can penetrate the outer membrane (hydrophobic) due to hydrophobic structure of the drugs, or they are taken up by bacteria *via* a porin-mediated process.



Vocab note: Remember that murein (older name) = peptidoglycan (newer name)

How do they cross the BBB?

Normally, beta lactams do not readily cross the BBB into CSF (too hydrophilic). HOWEVER, during meningeal inflammation, intercellular tight junctions separate and drug efflux pump activity slows, allowing CSF accumulation of beta lactams. Treatment to resolve the infection attenuates these mechanisms and slows drug entry into CSF. From UptoDate (08/2025):

- "Thus, maximal parenteral doses should be continued throughout the course of therapy to maintain adequate CSF concentrations.
- Antibiotic entry is also enhanced with drugs that have a
  - high lipid solubility
  - low molecular weight
  - low protein binding
  - low ionization at physiologic pH
    - i.e., all the molecular properties that tend to promote diffusion across a phospholipid membrane – it's not magic, just molecules doing their thing!

Route of Administration:

- IV (intravenous) delivery preferred in almost all cases
  - **Why???** CSF penetration of most antibiotics is already limited; oral dosing for meningitis yields much lower concentrations at sites of action
- Parenteral dosing should be kept HIGH (see directly above) as infection subsides
  - **Why???** Because initial inflammation helps to create drug permeability during the early stages of treatment; as treatment continues, inflammation (and drug penetration) decreases, requiring high circulating concentrations to maintain high CSF concentrations

Spectrum of activity:

- Most cell wall synthesis inhibitors, especially traditional PCN, are active against G(+)
- Extended-spectrum (ES) PCN (e.g., ampicillin, amoxicillin) are active against both G(+) and G(-)
- 3rd gen. cephalosporins are more active against G(-) bacteria and many can cross BBB.
- Aminoglycosides (30S ribosome inhibitors) are generally active against G(-) only.

Major side effects:

- Beta-lactams: allergy/ hypersensitivity rxn.
- Aminoglycosides: ototoxicity and nephrotoxicity

Notes by drug class:

- All beta lactams **mimic D-Ala-D-Ala** (a key component during bacterial cell wall synthesis) and **inhibit bacterial transpeptidase (PBP)** through competitive inhibition, leading to disruption of cross-linking process during peptidoglycan synthesis.
- The non beta-lactam vancomycin **binds to D-Ala-D-Ala**, blocking peptidoglycan synthesis.
- Aminoglycosides alone are ineffective against:
    - Anaerobes: uptake by bacteria requires a protonmotive force, usually generated in cells by an electron transport chain, which requires O_2. Anaerobes do not not generate a pmf, and therefore do not take up aminoglycosides
    - (G+) bacteria: aminoglycosides are bigger molecules than e.g., PCNs, and do not readily penetrate the murein layer.
        - However, combined with a cell wall synthesis inhibitor to disrupt integrity of the murein layer, aminoglycosides CAN effectively penetrate these bacterial cells.

Sources:

- UptoDate, accessed 2025-08
- Katzung