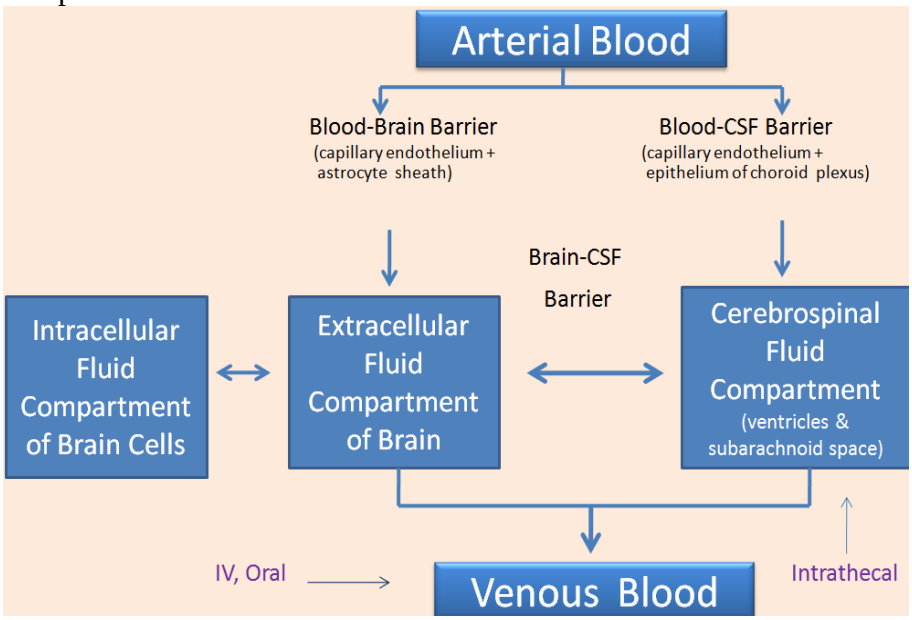
- **How (antimicrobial) drugs reach the brain?**
  - **Blood-brain barrier** (which is composed of non-fenestrated capillary endothelium + astrocyte sheath) has tight junctions which will not allow all molecules to cross from blood to the brain
  - **Blood-CSF barrier** (which is composed of fenestrated capillary endothelium + ependymal cells of choroid plexus)
  - **Generally, drugs are usually given intravenously or orally (and sometimes intrathecally: used less frequently nowadays).**
    - ✓ Intrathecally-administered drugs are directly introduced to ventricles (as a result the drug will get into the cerebrospinal fluid CSF).
    - ✓ Intravenously administered drugs (most common in case of meningitis): they get into venous blood →entering systemic circulation → and eventually reaching arterial blood supply of the brain → from there, there are 2 possible pathways for the drug:
      - ❖ *Either entering extracellular fluid compartment* of the brain through blood-brain barrier.
      - ❖ *Or entering cerebrospinal fluid compartment* through blood-CSF barrier.

      Note: drugs can move between extracellular fluid and CSF through brain-CSF barrier and depending on concentration gradient. Drug will also diffuse from between extracellular fluid and intracellular fluid compartment of brain cells.



- **Factors influencing passage of drugs from blood into brain/CSF:**
  - **Molecular weight**: small molecules pass more easily than large molecules. Fortunately, most of antimicrobial drugs are low-molecular drugs.
  - **Protein binding**: greater the protein binding inverses the relation of how effectively a molecule can get across the blood-brain barrier.
  - **Lipid/water partition coefficient (lipid solubility):** greater is the lipid solubility the more easier for the molecule to get across the blood-brain barrier.
  - **pKa (ionization constant):** greater is the unionized form → more lipid solubility.
  - **Status of meninges**: whenever there is meningeal inflammation, even those drugs with modest permeability can have a good therapeutic effect. At birth, blood-brain barrier is not fully functional (it takes several weeks to reach the adult level of maturation) → thus a newborn baby will have increased permeability of the meninges.

- **Principles of treatment in meningitis:**
  - **Blood and CSF samples are obtained before starting treatment.**
  - **In acute meningitis, antibiotics are almost always given intravenously (IV).** An exception is tuberculosis in which treatment is orally
  - **After patient becomes afebrile, treatment is recommended to be continued for 1 week.**
    - ✓ In pneumococcal meningitis: it is continued for 2 weeks.
    - ✓ In gram-negative infections: it is continued for 3 weeks.
  - **General management of complications:**
    - ✓ Maintaining fluid balance, prevention of aspiration and maintinence of patent airway.
    - ✓ Treatment of convulsion (using anti-convulsants with least effect in producing respiratory depression). Example: lorazepam.
    - ✓ Treatment of cerebral edema (which results from inflammatory process): by giving mannitol and corticosteroids (especially dexamethasone).
    - ✓ Treatment of headache: by analgesics.
- **Therapeutic issues pertinent to drug management of meningitis:**
  - Passage of antimicrobials is increased with presence of meningeal inflammation (inflammation increases permeability of antimicrobials such as penicillin).
  - Concomitant (المُصاحب) steroid therapy can alter passage of certain antimicrobials (such as penicillins and aminoglycosides) across the blood-brain barrier.
  - **Antimicrobial(s) choice is based on antimicrobial spectrum and the ability of antimicrobial to achieve sufficient concentration in the brain/CSF:**
    - ❖ Very good: metronidazole (very useful to treat brain abscess because it is achieving much higher concentration in the abscess that in blood).
    - ❖ Good: penicillins and cephalosporins (recommendations for meningitis are limited with 3rd generation cephalosporins).
    - ❖ Fair/poor: aminoglycosides, clindamycin, macrolides (azithromycin is the only macrolide which is used for meningitis) and vancomycin (has an important role especially in empiric therapy of meningitis).
- **Empiric therapy for bacterial meningitis:**

Age group/predisposition	Recommended therapy
Neonate (up to 2 months of age)	Ampicillin + cefotaxime
Infants and children (2-5 years)	Cefotaxime + vancomycin
Older children and adults	Cefotaxime + vancomycin
Elderly (+50 years)	Cefotaxime + vancomycin
Post-neurosurgical procedure	Ceftazidime + vancomycin
Closed head trauma	Cefotaxime + vancomycin
Open head trauma	Ceftazidime + vancomycin

- **Definitive therapy for bacterial meningitis:**

Pathogen	Recommended treatment
H.influenzae: • **β-lactamase negative** • **β-lactamase positive**	 Ampicillin Cefotaxime
N.meningitidis: • **Penicillin-sensitive** • **Penicillin-resistant**	 Penicillin G or ampicillin Cefotaxime
Strep.pneumoniae: • **Penicillin-sensitive** • **Penicillin-resistant**	 Penicillin G or ampicillin Cefotaxime + vancomycin
Strep.agalactiae	Penicillin G/ampicillin + gentamycin
L.monocytogenes	Penicillin G/ampicillin ± gentamycin
Enterobacteriaceae	

• **E.coli, Klebsiella** • **Enterobacter, serratia**	Cefotaxime Cefepime
P.aeruginosa	Cefepime
S.aureus: • **MSSA** • **MRSA**	Naficillin or oxacillin. Vancomycin ± rifampin
Staph.epidermidis	Vancomycin ± rifampin

- **Corticosteroid (dexamethasone) therapy in meningitis:**

Age groups	Causative organisms	Outcomes
Infants/children	S.pneumoniae	Controversial
Children	H.influenzae	Decrease neurologic sequelae especially hearing loss
Adolescents/adults	Mycobacterium tuberculosis	Improves survival but not severe disability
Adults	S.pneumoniae	Better outcome
All age groups	N.meningitidis, fungi anf viruses	No evidence supports a decrease in neurologic sequelae.

- **Note: rationale against corticosteroid use:**
  - ✓ Decreased passage of some antimicrobials across blood-brain barrier.
  - ✓ Increased incidence of GI-bleeding.

- **Prevention of meningitis (chemoprophylaxis):**
  - **Patients with CSF-rhinorrhea or CSF-otorrhea**: oral penicillin-V (500mg till leak stops).
  - **Close contacts of meningococcal meningitis**: rifampin 600mg for 2 days.
  - **Pregnant women (in whom rifampin is contraindicated) and children**: ceftriaxone.
- **Tuberculous meningitis:**
  - **Isoniazide, rafmpicin, pyrazinamide and ethambutol → for 2 months.**
  - **Followed by: isoniazide + rifampin → for 10 months.**
    Note: prednisone (it is a prodrug which is hydroxylated to prednisolone in the liver) may be required in tuberculous meningitis if there is:
    - ✓ *Spinal block.*
    - ✓ *Raised intracranial pressure.*
    - ✓ *Neurological signs.*
    - ✓ *High CSF protein levels.*
- **Herpes encephalitis: intravenous acyclovir (for 10 days).**