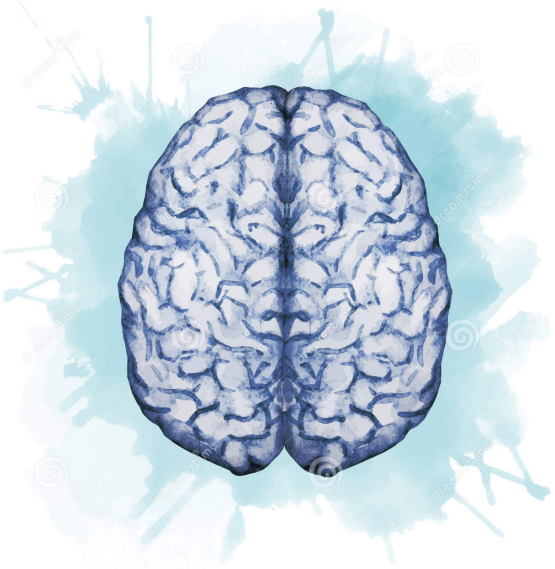
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



Drugs Used In Meningitis

Objectives:

- Describe briefly common types of meningitis.
- List the name of antibiotics used for treatment of meningitis
- Describe the principles of treatment.
- Describe the mechanism of action & adverse effects of the individual drugs.

color index:

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

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Check out the mnemonics file :
https://docs.google.com/presentation/d/1Z0Vf9oEOJSXo4JIA0mTCk5jB-OU9LP5TFCwz8iBgNac/edit?usp=sharing

Kindly check the editing file before studying this document
https://docs.google.com/presentation/d/1_-g1vol4eBWPet5xVCkuTGFvvnhFF3PJmU0tWtEEw_o/edit?usp=sharing

Introduction

Meningitis

It is an **inflammation** of the protective membranes covering **the brain and the spinal cord** (meninges).

Causes

Infectious	Non-Infectious
1.Viruses. (common). **2.Bacteria. (common).** 3.Fungal.	e.g. malignant meningitis (spread of cancer to meninges)

Bacterial Meningitis

Is a serious, **life threatening disease**. Without treatment, bacterial meningitis can cause **serious consequences**

- Cognitive deficits.
- Deafness. (loss of hearing)
- Hydrocephalus.
- paralysis.
- stroke, seizures, sepsis, and even death.

Causes of Bacterial Meningitis

- **Neisseria meningitidis.** (gram -ve)
- **Streptococcus pneumoniae.** Most common cause (gram +ve)
- Haemophilus influenzae. (gram -ve) ,Vaccine is available.
- Pseudomonas aeruginosa→(gram -ve),(**very resistant organism**)
- Staphylococcus aureus. (Gram +ve)
- Listeria Monocytogenes.
- Mycobacterium tuberculosis→ (tuberculous meningitis).

Route of transmission:

- The bacteria are carried by humans in the nose and throat and spread by close contact such as **coughing and/or sneezing, kissing, sharing eating utensils.**
- The pathogens spread from the **respiratory (main rout of transmission)** tract to the **blood stream** (**septicemia**) and to the nervous system and cause **bacterial meningitis.**
- Contaminated food specially in **immunocompromised patients and pregnant women**

Symptoms of Bacterial meningitis

- **High fever.**
- **Severe headache.**
- **Stiff neck.**

These 3 are meningitis triad

- Vomiting.
- Nausea.
- Seizure
- Irritability
- Sensitivity to bright light (photophobia) it is an alarm to meningitis
- Confusion.
- a rash of purple discoloration.

Treatment principles

Emergency hospitalization		Measures for treatment of complications.

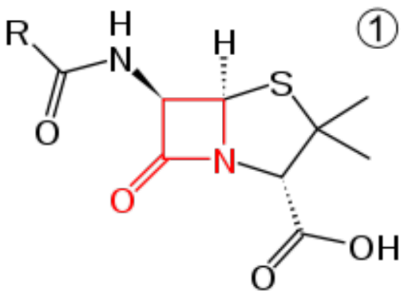
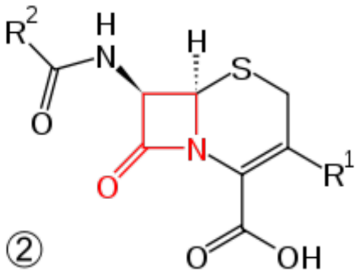
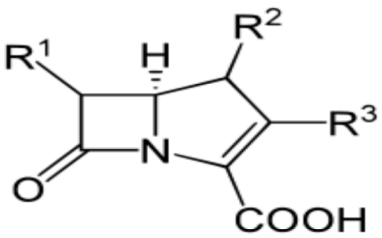
- **Antibiotics:** the most important characteristic of the selected antibiotic is to cross BBB(lipophilic drug) BUT inflammation of the meninges (meningitis) causes changes in the permeability so sometimes we can use hydrophilic drugs(polar) e.g.: aminoglycosides
- **Antibiotics Selected *must penetrate adequately into the CSF***
  Remember penetration is easier because of the inflammation.
- Regimen chosen must have **potent activity against known or suspected pathogens** & exert a bactericidal effect. (**Empiric**) mostly broad spectrum.

Prevention better than cure !

A) Haemophilus influenza type B (Hib) bacterium, a leading cause of bacterial meningitis **in children**. **So** there is a **New Hib vaccines** — available as part of the routine childhood immunization schedule have greatly reduced cases of this type of meningitis.	**B) Pneumococcal polysaccharide vaccine (PPSV)** for **older children and adults (protects against meningitis caused by S.pneumonia)**	**C) Meningococcal conjugate vaccine** ,people going to **Hajj**. **(protects against meningitis caused by N. meningitides)**

Because meningitis can be deadly we start empiric therapy (Treatment without exact diagnosis) Immediately. antibiotics are given to a person before the specific microorganism causing an infection is known. Empiric therapy may be changed after the culture sensitivity reports are available. Antibiotic selected must reach the meninges in a adequate quantities.

Antibiotics for treatment of Bacterial Meningitis

Mechanism: Inhibitors of cell wall synthesis (B-Lactams)		
Penicillins **Penams**	**Cephalosporins** **Cephems**	**Carbapenems**
		

- As you see here, that all β-lactam antibiotics share the β-lactam ring, but they differ by the compounds bound to it.
- Note the site where the Lactamase enzyme acting on. It called (beta-Lactam)ase, because it acts on beta-lactam ring and destruct it. β-lactamase production is the most common mechanism by which the resistance to penicillin developed. →That's why it is better to combine β- lactamase inhibitors with penincillins (e.g. **Amoxicillin + Clavulanic acid**) - The **penicillins** are susceptible to bacterial metabolism and inactivation by amidases and lactamases at the points shown in the figure.
- Note the beta-lactam chemical structure of **Carpenems**, there is stereochemical configuration in the lactam ring that imparts resistance to most common β lactamases.

How does the resistance developed with the penicillins & other beta-lactam antibiotic? Resistance to **penicillins** and other β-lactams is due to one of four general mechanisms:
(1) inactivation of antibiotic by β-lactamase
(2) modification of target PBPs (structure in the cytoplasmic mem of the bacteria)
(3) impaired penetration of drug to target PBPs,
(4) efflux. Beta-lactamase production is the most common mechanism of resistance

Penicillins

Spectrum	**Narrow Spectrum**	**Extended or wide (active against gram +ve and –ve)**	
Drug	**Penicillin G (benzyl penicillin)** natural penicillin	**Aminopenicillins** synthetic penicillin	
		Amoxicillin	**Ampicillin**
MOA	Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall **(bactericidal)**		
Pharmacokinetics	• **Poor oral absorption** • destroyed by **gastric acidity.** • Given **IV never orally because it can't cope with gastric acidity** • Short acting (4-6 hrs.) → the half-life of penicillin G can be increased to 10 hours in the presence of renal dysfunction. **Probenecid** inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels • β- lactamase sensitive(penicillinase sensitive)= they are susceptible to hydrolysis by β-lactamases • Half- life 30-60 min.	• Broad spectrum of activity than penicillin G • They are **acid stable** (effective **orally**) • **Can also be given parenterally (I.V or I.M)** • **Amoxicillin** is **better** absorbed from the **gut** and **not affected by food.** • **Ampicillin** is better to take it on empty stomach because of food drug interaction • ***Not active against pseudomonas aeruginosa*** → because Pseudomonas aeruginosa has restrictive porins (proteins inserted in the lipopolysaccharide layer), making this organism intrinsically resistant to many antimicrobial agents	
β -lactamase	-	• Inactivated by **β-lactamase enzyme**. (now a days combination with **B-lactamase inhibitors** are available e.g. **1- Amoxicillin + Clavulanic acid = Augmentin (given orally).** **2- Ampicillin + salbactum = Unasyn. (Injection).** • This combination is intended to: 1. Prevent enzymatic hydrolysis by **β-lactamase**. 2. Extend antimicrobial activity.	
ADRs	- • **Hypersensitivity** (**anaphylactic reaction**) → make sure that patient doesn't have allergy from the beta-lavtam antibiotics before giving him the treatment. Mild→ such as skin rash ,release of histamine and hypotension or sever →anaphylactic reaction • **Antibiotic-associated diarrhea** (only if taken orally) → the normal flora dies → Super infection mainly by clostridium difficile in colon. • **Nephritis** (with high doses). → beta lactam antibiotics (such as penicillin's) excreted mainly by kidney. • **Super-infections or secondary infections** (candidiasis, oral thrush). oral thrush happen especially in children after long term broad spectrum antibiotic course(normal flora died) and it is a fungal infection • **High dose in renal failure (seizure).** → high toxicity caused by renal failure → may cause seizure.		
Extra	• **Ampicillin** (with or without the addition of gentamicin) is the drug of choice for the gram-positive bacillus **Listeria monocytogenes.**		

Drugs	Cephalosporins (3rd generation)	Carbapenems
	Ceftazidime + Ceftriaxone	**Imipenem**
MOA	Inhibits bacterial cell wall synthesis **(Bactericidal)**	
Pharmacokinetics	Both of them are given by **intravenous infusion.**	• Not absorbed orally (**because it is NOT lipophylic instead it is hydrophilic BUT can cross BBB**) given by **I.V.** • **Penetrates body tissues and fluids including CSF**. • Excreted primarily by the kidney. • ***Doses must be reduced in renal failure***. • **Short** Half- life about 1 hr. • **Inactivated** by **dehydropeptidase** in renal tubules to a **nephrotoxic metabolites**, so it is given with a **dehydropeptidase inhibitor *Cilastatin*** for clinical use it given by combination of ***(Imipenem/cilastatin).*** • **Meropenem is one of carbapenems but doesn't cause renal toxicity s**
Bacterial spectrum	• **Highly effective against Gm –ve bacilli.** • Anaerobic microbes • **Ceftazidime** → **against pseudomonas aeruginosa.** • **Highly resistant to β- lactamases**→ **Ceftriaxone and cefotaxime** are approved for treatment of **meningitis.** • **Used for treatment of bacterial meningitis caused by(gram –ve organisms) *pneumococci*, *meningococci*, and *Haemophilus influenzae*.**	• Has a **wide spectrum** of activity (aerobic & anaerobic **gram negative** and **gram positive** bacteria, including **pseudomonads**). • ***Resistant to most β-lactamases.***
ADRs	• **Allergy** if the patient is allergic to penicillin he will be allergic to Cephalosporins**.** • **Thrombophlebitis at site of injection.** • **Renal toxicity.** • **Super-infection.** • **GIT Upset & diarrhea.** (not characteristic)	• **Nausea, vomiting, diarrhea.** • **Skin rash and reaction at the site of infusion.** • **High doses may cause seizure in patients with renal failure.** • **Patients allergic to Penicillins may be allergic to Carbapenems.**

Drug	Other inhibitor of cell wall synthesis	AMINOGLYCOSIDES
	Vancomycin	**Gentamicin**
MOA	Inhibits bacterial cell wall synthesis **(Bactericidal) it is not beta lactam**	**Inhibit protein synthesis (30s subunit) (Bactericidal)**
Pharmacokinetics	• **Poorly** absorbed **orally.** • Used **orally only** to treat **GIT infections** caused by **clostridium difficile** e.g. **pseudomembranous colitis** because it will stay in GIT and wont move anywhere else and **excreted in feces.** • Given **intravenously** for the treatment of **meningitis.**	• **Not absorbed orally** • **Given by injection I.V** **Remember**: all antibiotics affects the protein synthesis are considered as bacteriostatic EXCEPT **aminoglycosides** are **bactericidal**.
Indications	• Used against Methicillin resistant S. aureus **(MRSA).** • Used when the patient is allergic or resistant to penicillin's. because it is against the same type of bacteria which is gram +ve	
ADRs	• **Ototoxicity** rare, but the administration with another ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of these toxicities. • **Nephrotoxicity** • **Phlebitis** (inflammation of a vein) at site of injection. • **Histamine** release Causes **Red man (red neck) syndrome** →not IgA mediated reaction. →you might administered anti-histamine to prevent histamine effects such as diphenhydramine. • **Hypotension** (minimized if injected slowly over 60 minutes) usually infusion of the drug takes 20 min. and this is the cause of hypotension.	• **Ototoxicity** • **Nephrotoxicity (direct related to serum concentration).** • **Neuromuscular blockade *(in very high dose).* Contraindicated in patient with myasthenia gravis.**
Spectrum	• **Active only against Gram +ve bacteria** • (narrow spectrum) • With the exception of Flavobacterium.	• Antibacterial spectrum. • Bacterial exclusive for aerobic G-bacteria.
Combinations	• Used in combination with **3rd generation Cephalosporins** for treatment of meningitis caused by **penicillin resistant pneumococci.**	
	• May be combined with **Ampicillin or Ceftazidime** as an **initial therapy (empiric therapy)** of meningitis in infant, elderly and immunocompromised patients. • **Ceftazidime is better than Ciftriaxone in child.**	
Note	• **S. pneumoniae is the main cause of community acquired pneumonia and meningitis in children and the elderly and immunocompromised patients**	

إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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