PHARMACOLOGY TEAM

Lecture : 9

Meningitis

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OBJECTIVES

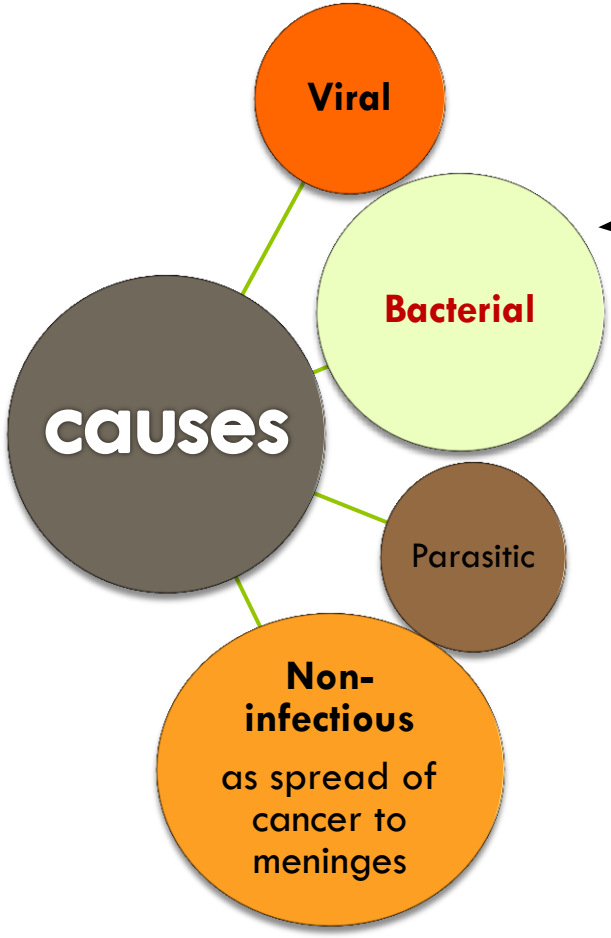
Students should :

1. Specify microorganisms causing meningitis
2. Delineate the therapeutic strategy
3. Classify the relevant antibiotics used
4. Expand on the pharmacokinetic and dynamic patterns of each antibiotic and specify its indications, contraindications& adverse effects.
5. List prophylactic measures taken against meningitis

Meningitis

Definition

Is an inflammation of the protective membranes covering the brain and the spinal cord .



IS A SERIOUS, LIFE –THREATING DISEASE THAT IS CAUSED BY AN INFECTION OF BACTERIA.

Such as

- Neisseria meningitidis
- Haemophilus influenzae
- Mycobacterium tuberculos-is
- Streptococcus pneumoniae
- Listeria monocytogenes

Slides | Important | Doctor's Notes | Explanation | Female's Slides

Bacterial Meningitis

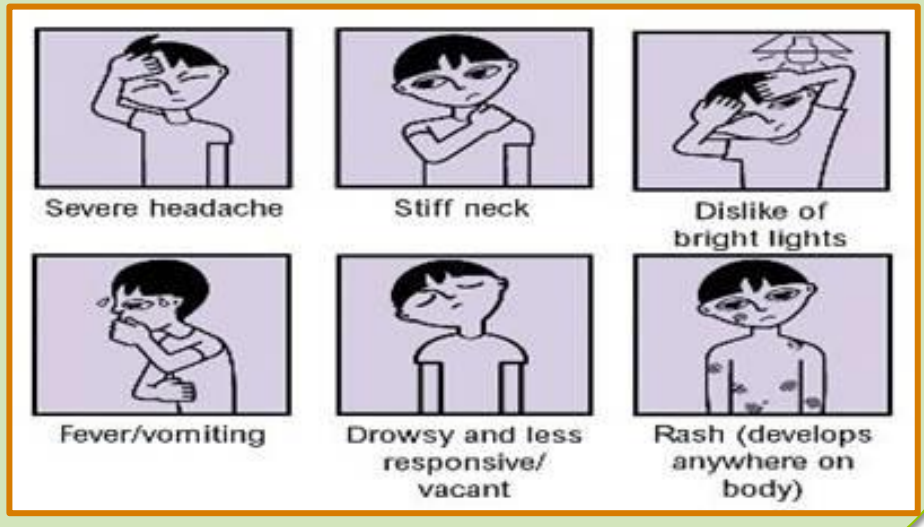
Route of transmission

The bacteria are carried by humans in the nose and throat (note that it's NOT normal flora) and spread into the air by coughing and/ or sneezing. They can be picked by anyone.

➔The pathogens spread from the respiratory tract to the blood stream and to the nervous system and cause bacterial meningitis .

SYMPTOMS OF BACTRIAL MENINGITIS

- Fever (very high fever)
- HEADACHE
- **STIFF NECK**
- IRRITABILITY To light
- NAUSEA & VOMITING



Bacterial Meningitis

TREATMENT PRINCIPLES:

- Emergency hospitalization
- Measures for treatment of complications
- Antibiotics

Note that narrow spectrum antibiotics are never used as empiric treatment (you must identify the organism first)

Empiric antibiotics

- **Treatment without exact diagnosis** (antibiotics are given to a person before the specific microorganism causing an infection is known –Never wait for the results-)
- Regimen chosen must have potent activity against known or suspected pathogens in a particular geographical place.
- Empiric therapy may be changed after the culture sensitivity reports are available.
- Antibiotic selected must reach the meninges in a adequate quantities.

- Meningitis
  - Antibiotics
    - Inhibitors of cell wall synthesis
      - β-Lactam Antibiotics
        - Penicillins
        - Cephalosporins
        - Carbapenems
      - Glycopeptides
        - Vancomycin
      - Aminoglycosides
        - Gentamicin
    - Inhibitors of DNA synthesis
      - Fluoroquinolones
        - Ciprofloxacin
  - Vaccines

Prevention better than cure

vaccines	for
NEW Haemophilus influenzae type b (Hib) vaccine	Haemophilus influenzae type b (**Hib**) bacterium, a leading **cause of bacterial meningitis in children**. In **routine childhood immunization,** greatly reduced cases of this type of meningitis.
Pneumococcal polysaccharide vaccine (PPSV)	**for older children and adults**
Meningococcal conjugate vaccine	**requirement for people going to Hajj.**

INHIBITORS OF CELL WALL SYNTHESIS

Drug family		Examples	Mechanism of action	Pharmacokinetics
β-Lactam Antibiotics				
PENICILLINS (Bactericidal)	Extended Spectrum	1. Amoxicillin 2. Ampicillin	Irreversibly inhibits transpeptidase enzyme that catalyze the final step in cell wall synthesis.(Inhibits the synthesis of peptidoglycan layer of bacterial cell wall)	•Amoxicillin and ampicillin are acid stable (effective orally) •Can also be given parentally (I.V or I.M) •Amoxicillin is better absorbed from the gut & not affected by food. (the only one in this group, others has to be taken on empty stomach)
	Narrow Spectrum	Penicillin G		•Destroyed by gastric acidity (so, it's given intravenously) •Short acting (4-6 hrs),inactivated by B-lactamases
Cephalosporins (Bactericidal)		3rd generation: 1. Ceftazidime 2. Ceftriaxone	Inhibits bacterial cell wall synthesis	•Both of them are given by intravenous injection •Ceftriaxone is excreted mainly through the biliary tract (it's the best drug for renal patients)
Carbapenems (Bctericidal)		Imipenem	inhibit bacterial cell wall synthesis.	•Not absorbed orally, taken by I.V.I. •Inactivated by dehydropeptidases in renal tubules, so it is -always- given with cilastatin (an inhibitor) for clinical use. •Penetrates body tissues and fluids including C.S.F.
Glycopeptides -Other inhibitor of cell wall synthesis- (non-β-Lactam Antibiotics)				
Glycopeptides (Bactericidal)		**Vancomycin**	Cell wall inhibitor	•Poorly absorbed orally •Used orally (only) to treat GIT infections caused by clostridium defficile e.g colitis. •Given intravenously

INHIBITORS OF CELL WALL SYNTHESIS

Drug family		Examples	Bacterial Spectrum
β-Lactam Antibiotics			
PENICILLINS (Bactericidal)	Extended Spectrum	1. Amoxicillin 2. Ampicillin	•Active against **gram +ve & gram -ve** microorganism. •**Inactivated by β- lactamase enzyme***, (nowadays combination with B-lactamase inhibitors are available e.g (Amoxicillin + Clavulanic acid)** and (ampicillin + sulbactam), are more effective against B-lactamase producing pathogens) (augmentin is the best empiric drug)
	Narrow Spectrum	Penicillin G	Inactivated by β- lactamase (No available combinations. Used mainly for meningococcal meningitis)
Cephalosporins (Bactericidal)		3rd generation: 1. Ceftazidime 2. Ceftriaxone	•Highly effective against **Gm –ve bacilli** •Anaerobic microbes •**Pseudomonas (ceftazidime)** •Highly resistant to β- lactamase
Carbapenems (Bctericidal)		Imipenem	•**Has a wide spectrum of activity** •Resistant to most β lactamases except metallo-β lactamase
Other inhibitor of cell wall synthesis (non-β-Lactam Antibiotics)			
Glycopeptides (Bactericidal)		**Vancomycin**	•Active only against **Gm+ve bacteria** •Used in combination with3rd generation cephalosporins for treatment of meningitis caused by penicillin resistant pneumococci. •Good drugs used against Methicillin*** resistant S. aureus (MRSA). •May be combined with ampicillin or ceftazidime as an initial therapy of meningitis in infant, elderly and immunocompromised patients .

Uesed in Gm-ve meningitis

*called penicillinase
**called Augmentin
***a preparation of penicillin

INHIBITORS OF CELL WALL SYNTHESIS

Drug family	Examples	Adverse effects
β-Lactam Antibiotics		
PENICILLINS (Bactericidal) – Extended Spectrum	1. Amoxicillin 2. Ampicillin	•Hypersensitivity •Diarrhea (not necessarly watery, also smooth) •Nephritis •Neurotoxicity •Hypersensitivity(rash,mild edmea, •articaria,anaphylactic shok gradually
PENICILLINS (Bactericidal) – Narrow Spectrum	Penicillin G	
Cephalosporins (Bactericidal)	3rd generation: 1. Ceftazidime 2. Ceftriaxone	•Allergy • Thrombophlebitis (from IV Injection) •Renal toxicity • Superinfections (because they kill normal flora –mouth ulcer is an example-)
Carbapenems (Bctericidal)	Imipenem	•Nausea, vomiting, diarrhea (very sever, doctor may stop the drug altogether!) •Skin rash and reaction at the site of infusion •High doses in patients with renal failure may lead to seizures •Patients allergic to penicillins may be allergic to carbapenems .
Glycopeptides (non-β-Lactam Antibiotics)		
Glycopeptides (Bactericidal)	**Vancomycin**	•Vancomycin is most toxic drug , used only when the infection is resistant to other safer drugs •Phlebitis •Ototoxicity could precipetate deafness and Nephrotoxicity,it appears with other group of antibiotics.Toxicity increases with aminoglycosides •Histamine release [red man (red neck) syndrome] (flushing and hypotension), minimized if injected slowly. •Hypotension

All β-Lactam Antibiotics have cross allergy. (when a patients has an allergic reaction against penicillin, he's most likely to have it against cephalpsporins & Carbapenems as well.

Toxicity increases with aminoglycosides

INHIBITORS OF DNA SYNTHESIS

Drug Family	Example	*Mechanism of action*	*Pharmacokinetics*
Fluoroquinolones Broad spectrum (Bactericidal)	***Ciprofloxacin***	**# Block bacterial DNA synthesis by inhibiting Bacterial *topoisomerase II* (*DNA gyrase*) & *topoisomerase IV*** was effective on a lot of organisms but it developed resistance bcuz of the frequent use	▸ Well absorbed orally ▸ Absorption is impaired by divalent cations ; iron, zinc or those in antacids as aluminium, magnesium ▸ Half-life 3hrs ▸ Widely distributed in body fluids & tissues ▸ Penetrates into CSF ▸ **Highly concentrated in bone, kidney, prostate, lung** ▸ Excreted through kidney & **appear in breast milk**

Bacterial Spectrum	*Adverse effects*	*Contraindications*
Effective against : ***Gm-ve organisms*** **Limited activity :** **against Gm+ve organisms** **Effective against:** intracellular pathogens such as: Legionella, Chlamydia, some mycobacteriae	▸ GIT upset ▸ CNS: Headache , dizziness, insomnia ➢ Abnormal liver function tests ➢ Skin rash & photosensitivity ➢ ***Cartilage damage (arthropathy) contraindicated in pregnant,lactating women and children*** ➢ Tendon damage (tendinitis) in adults ➢ Enzyme inhibitor	○ ***Growing children (below 18 years)*** ○ Pregnancy ○ Lactation ○ History of epilepsy or CNS disorder

Antibiotics For Treatment Of Bacterial Meningitis

1. Cephalosporins:
   eg; Ceftriaxone, i.v; Cefotaxime, i.v, Ceftazidime,i.v
2. Penicillins:
   eg; Penicillin G, i.v; Ampicillin, i.v; Amoxicillin i.v
3. Glycopeptides:
   eg; Vancomycin, i.v
4. Aminoglycosides:
   eg; Gentamicin, i.v
5. *Fluoroquinolones:*
   eg; Ciprofloxacin
6. Carbapenems
   eg; Imipenem

Drug Family	Examples	Mechanism Of Action	Adverse Effects
Aminoglycosides Bactericidal (Exclusive For Aerobic G- Bacteria).	**Gentamicin** This is mentioned in male's slides	Inhibit Protein Synthesis (30s Subunit)	Ototoxicity & Nephrotoxicity (Directly Related To Serum Conc). Neuromuscular Blockade (Very High Dose)

SUMMARY

- All the drugs mentioned here for meningitis are *bactericidal*.
- Ciprofloxacin is highly concentrated in bone (*not for children give arthropathy*), kidney, prostate, lung.
- *Hypersensitivity (allergy)* is side effect of all β-Lactam Antibiotics. So it prefer to give *Fluoroquinolones* or *Vancomycin.*
- *Amoxicillin* is the only penicillin drug not affected by food (doesn't matter if its empty or full stomach).

Mechanism of action	Drug	Effected organisims
Inhibits cell wall synthesis (β-Lactam Antibiotics)	**PENICILLINS +/- β-lactamase inhibitors**	**gram +ve & gram -ve**
	Cephalosporins (3rd generation)	**Gm –ve bacilli only!**
	Carbapenems	**wide spectrum of activity** (Resistant to most β-lactamases)
Inhibits cell wall synthesis (Non-β-Lactam Antibiotics)	**Vancomycin**	**Gm+ve bacteria only!**
Inhibits DNA synthesis	*Fluoroquinolones*	**Gm –ve & Gm+ve(limited)** intracellular pathogens

QUESTIONS

Q1) Penicillins mechanism of action is:

A. inhibits transpeptidase
B. inhibiting Bacterial topoisomerase 11
C. Inhibit bacterial DNA synthesis

Q2) best broad spectrum drug to give in empiric treatment:

A. Augmentin
B. Amoxicillin
C. Ampicillin

Q3) one of Penicillins drugs not affected by food (doesn't matter empty or full stomach) :

A. Ampicillin
B. Amoxicillin
C. Penicillin G

Q4) Used for meningococcal meningitis:

A. Ampicillin
B. Amoxicillin
C. ceftriaxone

Q5) which of these drugs most effective on Pseudomonas:

A. Ceftriaxone
B. Ceftazidime
C. Imipenem

Q6) Cephalosporins works on:

A. Both Gm-ve & Gm+ve
B. Gm+ve only
C. Gm-ve only

Q7) patient with cross allergy best drug to give is:

A. Ceftazidime
B. Ciprofloxacin
C. Imipenem

Q8) arthropathy is side effect of:

A. Ciprofloxacin
B. Ceftazidime
C. Augmentin

Q1) A
Q2) A
Q3) B
Q4) C
Q5) B
Q6) C
Q7) B
Q8) A

THE END

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