Revised & Approved

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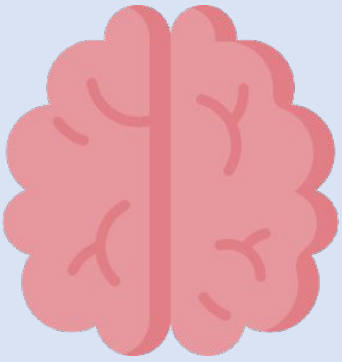
Pharmacology 439

MED439



Neuropsychiatry Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Meningitis

Objectives:

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

Editing file

Meningitis

An inflammation of the protective membranes covering the brain and spinal cord (meninges).

Causes of meningitis

Infectious:

- Bacterial
- Viruses
- Fungal

Non-infectious:

- Inflammatory disease (SLE)
- Cancer (malignant meningitis)
- Trauma to head or spine

Bacterial meningitis

A serious, life threatening disease May lead to serious consequences without treatment
(e.g. deafness,limb loss,epilepsy,paralysis,hydrocephalus,cognitive deficits,stroke,seizures,sepsis and even death)

Causes of bacterial meningitis

Most common cause:

1. Streptococcus pneumoniae (pneumococcal). Gram +ve
2. Neisseria meningitidis (meningococcal). Gram -ve

Other causes :

1. Haemophilus influenzae.
2. Staphylococcus aureus.
3. Pseudomonas aeruginosa.[1]
4. Listeria monocytogenes.
5. Mycobacterium tuberculosis—(tuberculous meningitis)

1. Hospital acquired and **very resistant** (known as "problematic bug")

Route of transmission

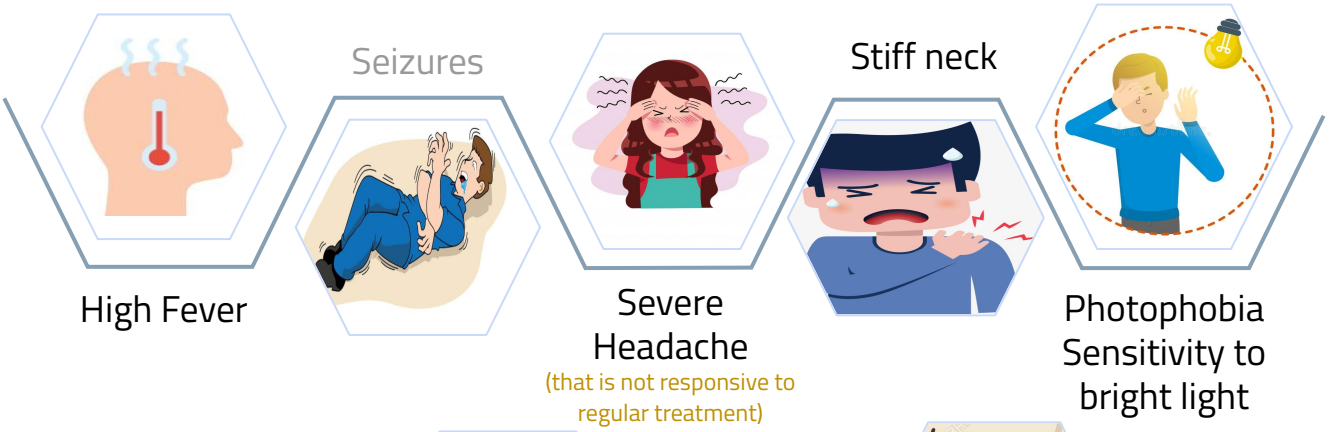
Most bacteria that cause form of infection are spread through close personal contact, such as:
coughing, sneezing, kissing

The pathogens spread from the respiratory tract to

Bloodstream (**septicemia**)

Nervous system and cause **bacterial meningitis**.

Symptoms of bacterial meningitis



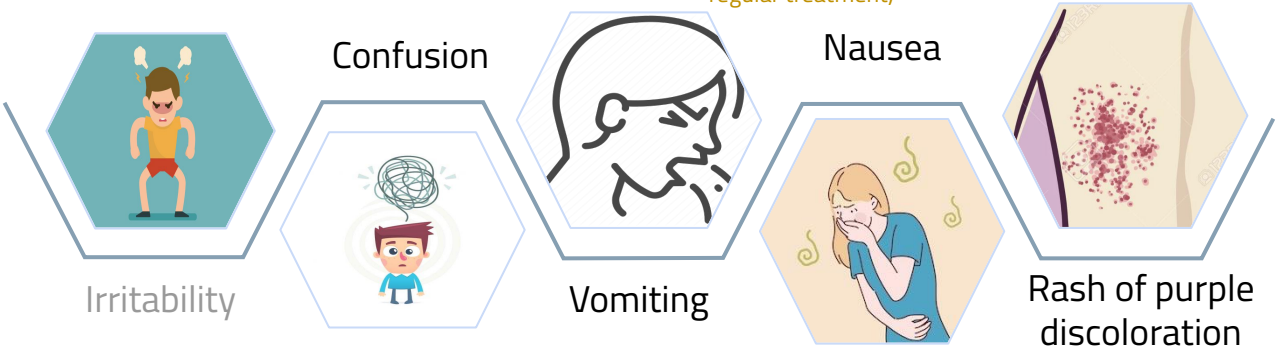
High Fever

Seizures

Severe Headache
(that is not responsive to regular treatment)

Stiff neck

Photophobia
Sensitivity to bright light



Irritability

Confusion

Vomiting

Nausea

Rash of purple discoloration
(especially seen with meningococcus)

Treatment principles

1. **Emergency hospitalization**
2. **Antibiotics:**
   A. Antibiotic selected penetrate adequately into CSF.
   B. Regimen chosen must have potent activity against known or suspected pathogens & bactericidal effect. (Empiric: cover gram +ve & -ve).
3. **Measures for treatment of conditions.**

Antibiotics for treatment of bacterial meningitis

If patient is allergic to penicillin then he's often allergic to carbapenems & cephalosporins as well.

Inhibitors of cell wall synthesis (B-lactamas) (first choice)

- Penicillins
  Penams
  (all penicillin derivatives)
- Carbapenem
  Last resort
- Cephalosporin
  Cephems
  Female Dr: (all cephalosporins derivatives)
  Male Dr: 3rd Gen Cephalosporins

Penicillins

Drug	Penicillin G (benzyl penicillin)	Aminopenicillin (Amoxicillin, Ampicillin)
M.O.A	Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall (bactericidal)	
P.k	• Poor oral absorption (destroyed by gastric acidity). mnemonic: G: avoid in Gut • Given IV infusion. • Short acting (4-6 hrs) • Half life 30-60 min. • β-lactamase sensitive (penicillinase sensitive).	• They are acid stable, not destroyed by gastric acid (effective orally) • Route of administration: I.V or I.M • Amoxicillin is better absorbed from gut and not affected by food. • Only drugs in this lecture with good oral absorption
Spectrum	Narrow (only gram +ve)	• Broad (against gram +ve and -ve • Not active against pseudomonas aeruginosa.
β-lactamase	–	Inactivated by β-lactamase enzyme. Combination with β-lactamase inhibitors are available: **1)** Amoxicillin + Clavulanic acid (Augmentin) = orally **2)** Ampicillin + Sulbactam (Unasyn) = IV This combination is intended to: • Prevent enzymatic hydrolysis by β-lactamase • Extend antimicrobial activity.
ADRs	• Hypersensitivity (anaphylactic reaction). Rash • Antibiotic associated diarrhea. May be mediated through alteration of intestinal microbiota, overgrowth of opportunistic pathogens, or direct toxicity. • Super-infections or secondary infections (candidiasis, oral thrush) When the normal microbiome is reduced, it provides an opportunity for pathogenic microbes to grow and potentially cause a new infection. • Nephritis. • High dose in renal failure **(seizure).**	

Cephalosporins (3rd Generation)

Drug	Ceftriaxone, ceftazidime, cefotaxime
M.O.A	Inhibit bacterial cell wall synthesis (bactericidal)
P.k	Given I.V by infusion.
Spectrum	• Highly effective against gram -ve bacilli • Highly resistant to β-lactamase. • Against Pseudomonas **(Ceftazidime)** • Bacterial meningitis caused by: pneumococci, meningococci, H. influenzae.
ADRs	• Thrombophlebitis at site of injection (to prevent it inject slowly) • Allergy • GIT upset and diarrhea • Super-infections • Renal toxicity

Carbapenems (Most powerful)

Drug	**Imipenem / Cilastatin**
M.O.A	Inhibits bacterial cell wall synthesis (bactericidal)
P.k	• Not absorbed orally, taken by I.V & Half- life about 1 hr. • Inactivated by **dehydropeptidase** in renal tubules to a less active & **nephrotoxic metabolites**, so it is given with a dehydropeptidase inhibitor cilastatin for clinical use → it is given by combination of imipenem + cilastatin. • Penetrates body tissues and fluids including CSF • Excreted primarily by the kidney. • Doses must be reduced in renal failure.
Spectrum	• Has a wide spectrum of activity (aerobic & anaerobic Gram+ve & -ve bacteria, **including pseudomonads**) mnemonic: C: Champion • Resistant to most β lactamases.
ADRs	• Skin rash & reaction at the site of infusion • Nausea, vomiting, diarrhea • Patients allergic to penicillins may be allergic to carbapenems • High doses may **cause seizure** in patients with renal failure (↓ dose to avoid)

Other inhibitor of cell wall synthesis

Drug	**Vancomycin**
M.O.A	Cell wall inhibitor (bactericidal)
P.k	• Poorly absorbed orally, only used orally to treat GIT infections caused by clostridium difficile e.g. pseudomembranous colitis. Poor oral absorption in this case is an advantage since we want a local effect without systemic ADRs. • Given I.V for the treatment of meningitis.
Spectrum	It is active only against gram +ve bacteria. (narrow spectrum)
Uses	• Used against Methicillin resistant S. aureus (MRSA). • 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 patient.
ADRs	• Ototoxicity especially with chronic use. • Nephrotoxicity • Phlebitis at the site of injection • **Histamine release due to nonspecific mast cell degranulation leading to:** (give antihistamines to minimize these effects) **1- Red man or Red neck syndrome**: anaphylactoid reaction caused by the rapid infusion of Vancomycin. RMS consists of a pruritic erythematous rash to the face, neck, and upper torso. due to flushing from histamine **2-** Hypotension (minimized if injected slowly over 60 minutes)

Aminoglycosides

Drug	Gentamicin
M.O.A	Inhibit protein synthesis (binding irreversibly to 30S subunit) (bactericidal)
P.k	- Not absorbed orally so given I.V - Used orally in very high doses before surgery to clear gut flora (local effect only like Vancomycin)
Spectrum	- Exclusive for aerobic Gram -ve bacteria - Can be combined with penicillin
ADRs	- Ototoxicity & Nephrotoxicity (directly related to serum conc.) - Neuromuscular blockade (very high dose or in renal failure) (paralysis).

Prevention better than cure

Haemophilus influenzae type b (Hib) vaccines
(protects against meningitis caused by Haemophilus influenzae type b bacterium)
- Hib causes bacterial meningitis in children.
- Vaccines available as part of the routine childhood immunization schedule have greatly reduced cases of this type of meningitis

Meningococcal conjugate vaccine
used for people going to Hajj (requirement)
(protects against meningitis caused by N. meningitidis)

Pneumococcal polysaccharide vaccine (PPSV)
for older children and adults
(protects against meningitis caused by S.pneumoniae)

Summary

Drug	Cell wall inhibitor					Inhibit protein synthesis (30s ribosomal subunit)
			Cephalosporins	Carbapenems		Aminoglycoside
	Penicillin G	Aminopenicillin (Amoxicillin, Ampicillin)	Ceftriaxone Ceftazidime Cefotaxime	Imipenem/ Cilastatin	Vancomycin	Gentamicin
spectrum	Narrow +ve	Broad +ve &-ve	Gram -ve bacilli	-ve &+ve aerobic and anaerobic	+ve MRSA	aerobic G-ve bacteria
ADRs	-Hypersensitivity (anaphylactic) -Diarrhea -Super infections or secondary infections -Nephritis -High dose in renal failure (seizure)		-Thrombophlebitis -Allergy -GIT upset -Super infections -Renal toxicity	-Nausea, vomiting, diarrhea -Skin rash -High dose in renal failure (seizure) -Patients allergic to penicillins may be allergic to carbapenems	-Ototoxicity -Nephrotoxicity - Phlebitis. at the site of injection - Histamine release leading to 1- Red man or Red neck S 2-Hypotension (minimized if injected slowly over 60 minutes)	-Ototoxicity -Nephrotoxicity -Neuromuscular blockade

MCQs

Q1: Which one is <u>not</u> a Symptom of bacterial meningitis ?			
A- Stiff neck	B- Photophobia	C- Vertigo	D- Fever
Q2: What is the mechanism of action of Gentamicin?			
A- Inhibiting synthesis of proteins	B- Inhibiting bacterial wall synthesis	C- Inhibiting nucleic acid synthesis	D- Alteration of cell membrane
Q3: Which one of these antibiotics could lead to anaphylactic reaction			
A- Penicillins	B- Aminoglycoside	C- Cephalosporins	D- Carbenems
Q4: If a patient took Vancomycin which one of these is the most adverse side effects?			
A- Bone marrow suppression	B- Anemia	C- Red man syndrome	D-Hepatotoxicity
Q5: Patient treated by antibiotic previously, now he is Suffering from ototoxicity and nephrotoxicity which one of these antibiotics could lead to those symptoms?			
A- Vancomycin	B- Gentamicin	C- Ceftriaxone	D-A &B
Q6: Prescribing HIGH dose Imipenem for patients with renal failure Cause :			
A- Seizure	B- Hepatitis	C- Hypertensive reaction	D- none
Q7: Imipenem Inactivated by dehydropeptidase in renal tubules to a nephrotoxic metabolites so we give:			
A- Penicillin	B- Cilastatin	C- Ceftazidime	D- Beta blocker
Q8: Which of the following can be used in case of Methicillin resistant S. aureus			
A- Ceftriaxone	B- Penicillin G	C- Vancomycin	D- Amoxicillin + Clavulanic Acid.
Q9: Which of the following is the drug of choice in cases of meningitis by pseudomonas aeruginosa ?			
A- Penicillin G.	B-Ceftriaxone	C-Amoxicillin + Clavulanic Acid.	D-Ceftazidime

1	2	3	4	5	6	7	8	9
C	A	A	C	D	A	B	C	D

SAQ

An 84-year-old woman is brought by her caretaker to the physician because of a 2-day history of fever(1), severe headache (2), neck pain(3), and aversion to bright light(4 photophobia). She appears uncomfortable(5 Irritability). Her temperature is 38.5°C (101.3° F), pulse is 110/min, and blood pressure is 145/75 mm Hg. Physical examination shows involuntary flexion of the bilateral hips and knees with passive flexion of the neck. Cerebrospinal fluid analysis shows a leukocyte count of 1200/mm3 (76% segmented neutrophils, 24% lymphocytes), a protein concentration of 113 mg/dL, and a glucose concentration of 21 mg/dL. A CT scan of the brain shows leptomeningeal enhancement. Use this case to answer the following two questions

Q1) Which is the most appropriate initial pharmacotherapy?

Q2) Enumerate 2 ADRs of drug you mentioned in previous question

Ahmad, an 8 year old boy, was suffering from a high fever and neck stiffness . When he woke up in the morning he also had a sudden headache and he was abnormally sensitive to bright light. He went to the emergency room and he was diagnosed with bacterial meningitis and doctor give him Amoxicillin + clavulanic acid. Ues this case to answer the following two questions

Q3) Describe this drug's mechanism of action

Q4) What is the reason behind the combination of drugs you mentioned above?

Answers

A1) Vancomycin, ampicillin, and ceftazidime

A2) Slide 4, 5 or check the summary

A3) Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall (bactericidal)

A4) Prevent enzymatic hydrolysis by β-lactamase, Extend antimicrobial activity.

Feedback Form

Neuropsychiatry Block

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