#9
Drugs used in Meningitis

Objectives:

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

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Meningitis

Definition:

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

Causes:

1- Infectious

- Viruses
- Bacteria
- Fungal

2- Non-infectious

e.g. spread of cancer to meninges (malignant meningitis) ,etc.

Bacterial meningitis:

- Is a serious , **life threatening disease**.
- May lead to serious long –term consequences (e.g. deafness, epilepsy, hydrocephalus & cognitive deficits).

CAUSES OF BACTERIAL MENINGITIS

- Neisseria meningitides.
- Streptococcus pneumoniae.
- Haemophilus influenza
→ **children**
- Staphylococcus aureus.
- Pseudomonas aeruginosae
→ (very resilient organism)
- Listeria monocytogenes.
- Mycobacterium Tuberculosis
→ (tuberculous meningitis)

Route of transmission:

- The bacteria are carried by humans in the nose and throat and spread by coughing and/or sneezing, kissing, sharing eating utensils.

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

Symptoms of bacterial meningitis:

Meningitis triad

- High fever
- Stiff neck
- Seizures
- Severe headache
- Irritability
- Vomiting

TREATMENT PRINCIPLES

- **Emergency hospitalization**
- **Antibiotics**

Antibiotic selected must **penetrate** adequately into the **CSF**.

- **Measures for treatment of complications**

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**.
ليه نعطيه ال empiric therapy وإحنا ما نعرف إيش الأورقانزم اللي سبب له المننجايتس؟
لأن هذي الحالة ممكن تكون مميتة لو ما لحقت على المريض، وعلى ما تطلع النتايج حقت الأورقانزم بتأخذ لها وقت ممكن المريض في هذا الوقت تسوء حالته وممكن يموت! لذلك لازم تلحق على مريضك، وتعطي أنتي بيوتك عنده wide spectrum عشان يغطي أغلب الأورقانزمز اللي منتشرة وغالبًا تسبب المننجايتس.

Regimen chosen must have potent activity against known or suspected pathogens & exert a bactericidal effect. (**Empiric**)

Signs and Symptoms of Meningitis

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**

C) Meningococcal conjugate vaccine ,people going to **Hajj**.

Extra

There are different types of meningitis, but the focus of this lecture is **Bacterial meningitis** and the antibiotics used for treatment.

Bacterial meningitis is contagious and caused by infection from certain bacteria. It's fatal if left untreated. Between 5 to 40% of children and 20 to 50% of adults with this condition die. This is true even with proper treatment.

Bacterial meningitis requires immediate hospitalization. Early diagnosis and treatment will prevent brain damage and death

So we start giving **empiric therapy** until the test results

Table 7. Recommended Empiric Antibiotics for Suspected Bacterial Meningitis, According to Age or Predisposing Factors[25] (Open Table in a new window)

Age or Predisposing Feature	Antibiotics
Age 0-4 wk	Ampicillin plus either cefotaxime or an aminoglycoside
Age 1 mo-50 y	Vancomycin plus cefotaxime or ceftriaxone*
Age >50 y	Vancomycin plus ampicillin plus ceftriaxone or cefotaxime plus vancomycin*
Impaired cellular immunity	Vancomycin plus ampicillin plus either cefepime or meropenem
Recurrent meningitis	Vancomycin plus cefotaxime or ceftriaxone
Basilar skull fracture	Vancomycin plus cefotaxime or ceftriaxone
Head trauma, neurosurgery, or CSF shunt	Vancomycin plus ceftazidime, cefepime, or meropenem

CSF = cerebrospinal fluid.

*Add ampicillin if *Listeria monocytogenes* is a suspected pathogen.

Bacterial Meningitis Treatment & Prevention, 10:53 min

To understand Better

Chemistry of β-lactam Antibiotics:

All information here are **extra**, but it is better to understand ☺

All penicillins have the basic structure, which Share the **β-lactam ring** shown in this figure.

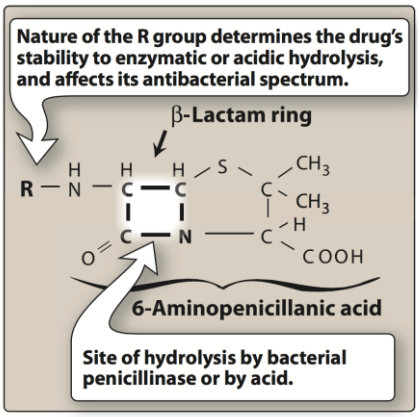
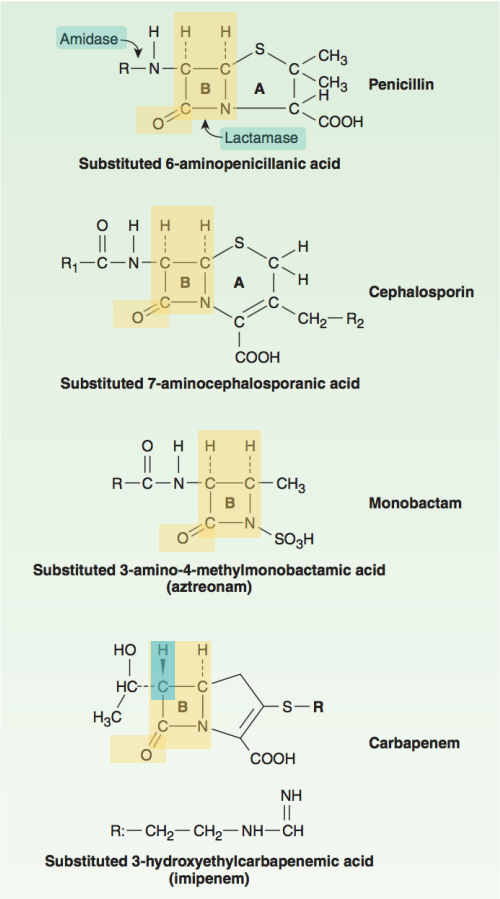


Figure 31.2
Structure of β-lactam antibiotics.

→ **So How do they differ from each other?**

And why their spectrum uses is different?

See the figure below:



- 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?

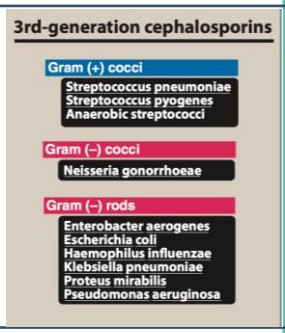
Resistance to penicillins and other β-lactams is due to one of four general mechanisms:
(1) inactivation of antibiotic by **β-lactamase**
(2) modification of target **PBPs** (structure in the cytoplasmic mem of the bacteria)
(3) impaired penetration of drug to target PBPs,
(4) efflux. Beta-lactamase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

PENICILLINS

Drug	Penicillin G (benzyl penicillin)	Aminopenicillins	
		Amoxicillin	Ampicillin
MOA	Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall (**bactericidal**).		
Spectrum	**Narrow** → (not used as empiric) → These have greatest activity against gram-positive organisms, gram-negative **cocci**, and non- β-lactamase producing anaerobes - Click here to know the therapeutic applications.	Extended or wide (against gram **+ve** and **–ve**)	
P.K	- **Poor oral** absorption → It destroyed by **gastric acidity.** - Short acting (4-6 hrs) → the half-life of penicillin G can increase 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. - Given **IV**. - **β- lactamase sensitive** (penicillinase sensitive) = they are susceptible to hydrolysis by β-lactamases	- They are **acid stable** (effective orally) - Rout of administration: **I.V** or **I.M** - **Amoxicillin** is **better** absorbed from the **gut** and not affected by food. - **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. given IV - This combination is intended to: - Prevent enzymatic **hydrolysis by β-lactamase**. - 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. Might be mild such as skin rash or sever anaphylactic reaction. - Antibiotic-associated **diarrhea** (only if taken orally) → the normal flora died → Super infection mainly by clostridium difficile in colon. - Nephritis (with high doses). → All penicillins are excreted by kidney - Super-infections or secondary infections (candidiasis, oral thrush) → normal flora died because the use of broad spectrum antibiotic - High dose in renal failure (seizure). → if there is high toxicity caused by renal failure → may cause seizure.		
Extra info.	- **Ampicillin** (with or without the addition of gentamicin) is the **drug of choice** for the gram-positive bacillus ***Listeria monocytogenes***.		

Cephalosporins (3rd generation)

Drug	Ceftriaxone / Ceftazidime
MOA	- Inhibit bacterial cell wall synthesis (bactericidal).
P.K	- Both of them are given by **intravenous** infusion.
Bacterial Spectrum	- Highly effective against Gm **–ve** bacilli. - Anaerobic microbes. - **Ceftazidime** → against ***P. aeruginosa***. - Highly **resistant to β- lactamases**.→ عشان كذا هو ما يحتاج نعطي معه بيتالاكتاميز انهيتورز - Ceftriaxone and cefotaxime are approved for treatment of **meningitis**.
ADRs	1- **Allergy** (rare but very serious). 2- **Thrombophlebitis** (at site of injection). 3- Renal toxicity. 4- Super-infections. 5- GIT upset & diarrhea. → bc of broad spectrum



Carbapenems

Drug	Imipenem
MOA	- Inhibits bacterial cell wall synthesis (bactericidal).
P.K	- Not absorbed orally, **taken by I.V**. **- Inactivated** by **dehydropeptidases** in renal tubules to a **nephrotoxic metabolites**, so it is given with an dehydropeptidases **inhibitor** cilastatin for clinical use. → it is given by combination of **imipenem + cilastatin.** - Penetrates body tissues and fluids including CSF.
Bacterial Spectrum	- Has a **wide spectrum** of activity (aerobic & anaerobic GM **+ve** & GM **-ve** bacteria, including **pseudomonads**). - **Resistant** to most β lactamases.
ADRs	- **Nausea, vomiting, diarrhea**. (GIT upset) - **Skin rash and reaction at the site of infusion**. → bc they are beta-lactam. - High doses may **cause seizure** in patients with renal failure (important and common adverse effect). - Patients allergic to penicillin's may be allergic to carbapenems .

Other inhibitor of cell wall synthesis

Drug	Vancomycin
Spectrum	With the exception of Flavobacterium, it is active **only** **against gram positive bacteria**. (narrow spectrum) → can not be administered alone especially as an empiric therapy.
MOA	Cell wall inhibitor (bactericidal)
P.K	- **Poorly** absorbed **orally**. - Used **orally** to treat **GIT infections** caused by *clostridium difficile* e.g. **pseudomembranous colitis**. The only **oral** use for it - Given intravenously for the treatment of **meningitis**.
Indications	- Used when the patient is allergic to penicillins. - Used against Methicillin resistant S. aureus **(MRSA).**
ADRs	**1- Phlebitis** at site of injection. 2- **Ototoxicity** → rare, but the administration with another ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of these toxicities. 3- **Histamine** release (flushing of upper body) → **red man** (red neck) **syndrome** → **not IgA mediated reaction. → you might administered anti-histamine to prevent histamine effects such as diphenhydramine.** 4- Nephrotoxicity 5- **hypotension** (minimized if injected **slowly** over 60 minutes).
COMBINATION	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** of meningitis in infant, elderly and immunocompromised patients.

Summary

Inhibitors of cell wall synthesis (β-lactams)

Group	Penicillin			Cephalosporin's 3rd generation.		Carbapenems
Drug	Penicillin G	Amoxicillin	Ampicillin	Ceftazidime.	Ceftriaxone.	Imipenem
Spectrum	Narrow	Active against gram +ve and –ve.		**Effective against:** gram –ve, anaerobic microbes, pseudomonas (ceftazidime)		**Effective against:** aerobic and anaerobic microbes, gram +ve and –ve including pseudomonas.
Mech. of Action	Inhibiting Peptidoglycan layer synthesis in the cell wall. (**Bacteriocidal**)			Inhibitors of cell wall synthesis (bactericidal)		
Affected by β-lactamase.	Yes			NO		
P.K	Destroyed by **gastric acidity**.	Acid stable. Effective orally. Can be given I.V or I.M.		IV **only**		IV
Combination	-	**Amoxicillin** + Clavulanic acid (inhibition of β lactams)	**ampicillin** + salbactum (inhibition of β latcams)	-		**Imipenem** + **cilastatin**
ADRS	- Hypersensitivity. - Diarrhea nephritis. - Neurotoxicity.			Allergy, **thrombophlebitis** at the site of injection, renal toxicity and superinfections		Seizures, GIT effects, **Skin rash** and reaction at the site of infusion.

Summary

Other Inhibitors of Cell Wall Synthesis

Drug	**Vancomycin**
Spectrum	Active only against gram **+ve** bacteria.
Mech. of Action	Cell wall inhibitor (Bactericidal).
P.K	**I.V** → meningitis Poorly absorbed orally.
Combination	- With **ampicillin** or **ceftazidime** as an initial therapy for **immunocompromised** patients. - With **3rd generation cephalosporin's** to treat meningitis caused by **penicillin resistant pneumococci**
ADRs	**Phlebitis** at site of injection, **ototoxicity**, **nephrotoxicity**, **histamine release** (red man syndrome) and **hypotension**.

Empiric therapy:

- In the Empiric therapy → Use antibiotics with **broad spectrum** → e.g. (Imipenem + Cilstaten), or (Amoxicillin or Ampicillin + beta-lactamase inhibitors)

* Vancomycin + Penicillin G → **not used alone as empiric therapy** because they have **narrow spectrum**.

Extra summary

- Very helpful in both pharmacology & microbiology!

TABLE 7-5. Empiric Antimicrobial Therapy for Acute Bacterial Meningitis

Patient Profile	Etiology	Empiric Treatment
Preterm to <1 month	*Streptococcus agalactiae* (group B streptococcus), *Escherichia coli*, *Listeria*	Ampicillin + cefotaxime or ampicillin + gentamicin
1 month to 50 years	*Streptococcus pneumoniae*, *Neisseria meningitidis*	Cefotaxime or ceftriaxone + vancomycin + dexamethasone*
Age >50 years, alcoholism, impaired cell-mediated immunity	*S pneumoniae*, *Listeria*, and gram-negative bacteria	Cefotaxime or ceftriaxone + ampicillin + vancomycin + dexamethasone

*Dexamethasone blocks tumor necrosis factor production and reduces inflammation.

TABLE 7-6. Specific Antimicrobial Therapy Used to Treat Acute Bacterial Meningitis

Organism	Treatment
Streptococcus pneumoniae	Penicillin G or vancomycin (for resistant strains)
Neisseria meningitidis	Penicillin G or chloramphenicol
Listeria monocytogenes	Ampicillin + gentamicin
Staphylococcus aureus Methicillin-sensitive *S aureus* (MSSA)	Nafcillin or oxacillin + rifampin
Methicillin-resistant *S aureus* (MRSA)	Vancomycin + rifampin (also used to treat *Staphylococcus epidermidis*)
Enterobacteriaceae	Ceftriaxone + gentamicin (intrathecal and systemic)

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Pharmacology 435

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دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
لينا إسماعيل
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Sources:
1- 435's Lecture.
2- http://www.healthline.com/health/meningitis#Prevention8
3- http://emedicine.medscape.com/article/232915treatment#d8
4- Pharmacology (Lippincotts Illustrated Reviews Series), Chapter 31, 5th edition.
5- Basic & Clinical Pharmacology by Katzung. Chapter 43, 12th edition
6- Medical microbiology, by Chamberlain.

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