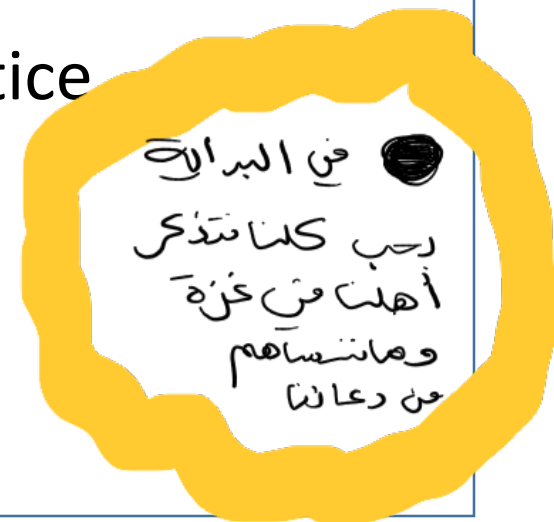


Cell wall synthesis inhibitors

Part 2

Pharmacology 3
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Faculty of Pharmaceutical Sciences
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II. CEPHALOSPORINS

هنا جدول لأي نوع من أنواع
Cell wall synthesis inhibitors

prefix : Cef or Ceph

- A wider spectrum than penicillins.
- More resistance to B-lactamase enzyme.
- Eliminated by kidney.
- More expensive than penicillins.

الـ *Renal* *excretion*
الـ *Renal* *excretion*

دواء *dose*
adjustment
Renal impairment

①

②

يعني ممكن بكثرة
عندما قدرة
الـ *penicillins*
بين ما عندنا
الـ *Cef*
تخطيم الـ *B-lactamase*
لأن الـ *B-lactamase*
إلى أنواع كثيرة من
الـ *B-lactamase*

Cephalosporins

Gram + activity

1st Generation

β -lactamase sensitive

2nd Generation

Gram — activity

3rd Generation

β -lactamase resistant

4th Generation: good Gram + and Gram - activity;
more resistant to β -lactamase

الجيل 1
عن 5th
generation
في الـ 1st
الجيل 2
في الـ 2nd
الجيل 3
في الـ 3rd
الجيل 4
في الـ 4th
more
Resistance
to β -lactamase

بـ 1
نـ 2
أـ 3
أـ 4

Summary of therapeutic applications of cephalosporins

کل عاصتہ

اکثری Generation 1

Coverage 3rd

Gram 1
اکثر (3rd)

First-generation cephalosporins

Gram (+) cocci

Staphylococcus aureus*
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci

Gram (-) rods

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

*Methicillin-resistant staphylococci are resistant

ماہی
اکثری
کٹھا
Resistant
MSSA
من جین
Cefaz

Second-generation cephalosporins

Gram (+) cocci

Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci

Gram (-) cocci

Nisseria gonorrhoeae

Gram (-) rods

Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis

Anaerobic organisms**

**Cefoxitin and cefotetan have anaerobic coverage

Third-generation cephalosporins

Gram (+) cocci

Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci

Gram (-) cocci

Nisseria gonorrhoeae

Gram (-) rods

Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Resistant کیں
anti-biotic
بڑھو لگا

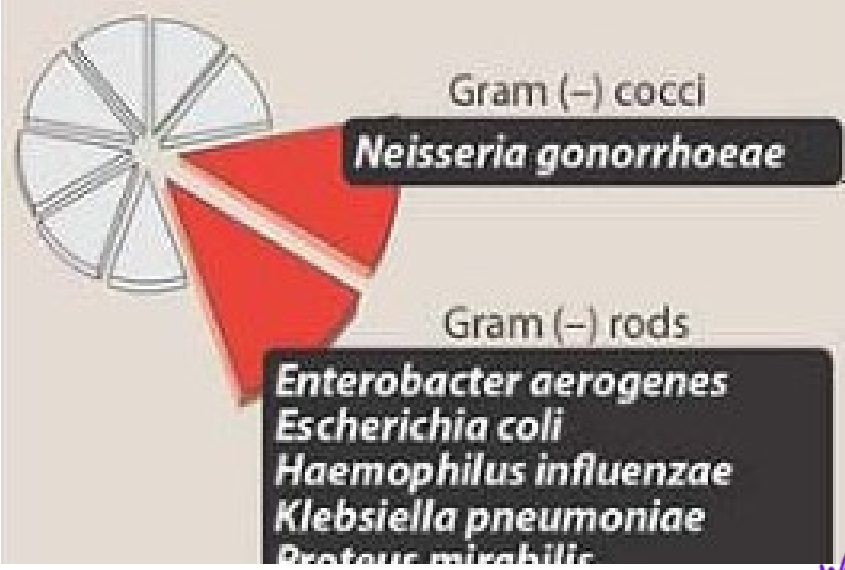
۵۱۰ الکتورج صحتی عن موقع
عستان نفی اکتی عن ال indication
اسم up to date

عستان هین
بنفسه عنی کلام
از کلام هین
meningitis

Third generation Cephalosporins

هسا لجا اده وهر بیکر کیر لا CNS

Third-generation cephalosporins



Adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with the **third-generation cephalosporins**.

Are effective in the treatment of neonatal and childhood **meningitis** caused by H.influenzae. meningococcal meningitis.

Third-generation cephalosporins must be used with caution, as they are associated with significant **"collateral damage,"** including the induction of antimicrobial resistance and development of Clostridium difficile infection.

یعنی هو بمل ال damage
ای لارم بمل و لکن بمل
کیر اکثر من ال لارم
damage
لقتل البکتر یا ال سیه خیر ای
infection

قتل ال
Normal flora
عستان هین بمل

Cephalosporins Active against Methicillin-Resistant Staphylococci (advanced generation; 5th generation)

MRSA

• **Ceftaroline.**

- The unique structure allows ceftaroline to bind to PBPs found in MRSA and penicillin-resistant Streptococcus pneumoniae.
- Ceftaroline is currently approved for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia.

Therapeutic advantages of some clinically useful cephalosporins

First Generation

Cefazolin ←

This first-generation parenteral cephalosporin has a longer duration of action and a similar spectrum of action, compared to other first-generation drugs. It penetrates well into bone.

Cefadroxil ←

Cephalexin ←

This is the prototype of first-generation, oral cephalosporins. Oral administration twice daily is effective against pharyngitis.

Second Generation

Cefuroxime sodium ←

This prototype second-generation, parenteral cephalosporin has a longer half-life than similar agents. It crosses the blood–brain barrier, and it can be used for community-acquired bronchitis or pneumonia in the elderly and for patients who are immunocompromised.

Cefuroxime axetil ←

Administered twice daily, this drug is well absorbed and is active against β -lactamase-producing organisms.

Third Generation

Cefdinir
Cefixime ←

These are administered orally once daily.

Cefotaxime ←

This penetrates well into the CSF.

Ceftazidime ←

This is active against *Pseudomonas aeruginosa*.

Ceftriaxone ←

This drug has the longest half-life of any cephalosporin (6 to 8 hours), which permits once-a-day dosing. High levels of the drug can be achieved in blood and CSF. It is effective against genital, anal, and pharyngeal penicillin-resistant *Neisseria gonorrhoeae*. The drug is excreted in bile and may be used in patients with renal insufficiency. It has good penetration into bone.

Fourth Generation

Cefepime ←

This is active against *Pseudomonas aeruginosa*.

Advanced Generation

Ceftaroline ←

This is active against MRSA.

ای و حقن
بالقوة
هما بيتا خذوا
orally



Pharmacokinetics

عوضهم

1. Administration:

- Many of them must be administered IV or IM because of their poor oral absorption (however some can be given orally)

2. Distribution:

- CPNs distribute very well into body fluids but not to CSF.

- Cefazolin** penetrates well into most tissues. It is a drug of choice for **surgical prophylaxis** including **orthopedic surgery** because of its ability to penetrate bone.

orthopedic surgery

- Only **ceftriaxone** or **cefotaxime** achieve therapeutic levels in the CSF and have become agents of choice for meningitis.

بوصلا الى CNS فقط

- All CPNs cross the placenta.

بوصلا ولكن
مستوى بكميات كبيرة

3. Elimination:

- Tubular secretion and/or glomerular filtration
- Doses must be adjusted in cases of renal failure

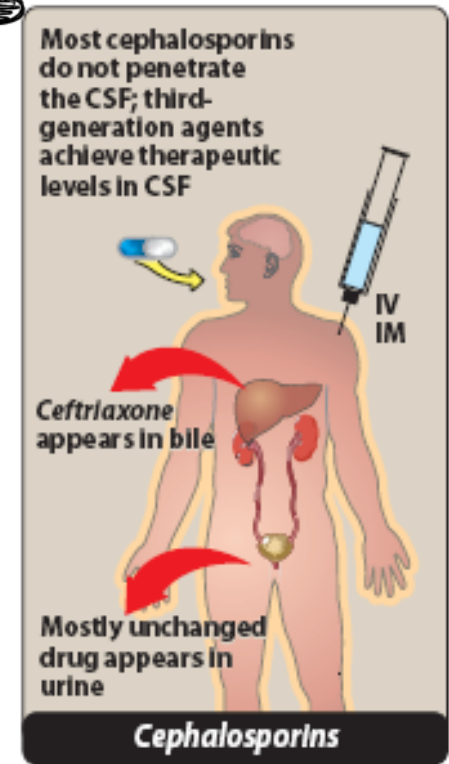
كلهم عن طريق ال Renal
ال ceftriaxone عن طريق ال
bone

- Exception: **Ceftriaxone**, excreted through the bile.... **Employed in patients with renal insufficiency**

فقداء بعض الكلى
Renal problem
dose adjustment
الباقي يحتاجوا

First generation

حسينا عنهم فوقه انه
عنهم قدرة كبيرة في
الوصول للعظميات
هين بعضهم في حالات ال



Adverse effects

* الحساسية بالغالب بتعبر
بسبب ال side chain (R-group)
مستجيب ال β -lactam

✓ Hypersensitivity reaction

Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β -lactam structure.

* يعني انه اذا كان عندك حساسية ببنسلين
مستجيب ببنسلين ممكن يكون عندك حساسية سيفالوسبورين

The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

يمكن الاستخاض اى كنده حساسية ببنسلين
لو حذرت سيفالوسبورين ولكن with caution

ال 1st generation cephalosporins
هو اى بيتشابه مع ال penicillin

Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.

بسي كى مستحق كنده allergy ال penicillin
لو كان عندك حساسية ال cephalo [لو اذا كان allergic يكون
من ال penicillins 1st]

Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins **should not receive cephalosporins**.

هي Reaction كيتخاطر
ال dermes بتفصل عن
ال dermes الثانية ويكون (very severe)

يفضل الاستخاض اى حذر
عنهم anaphylactic من استخاضهم
ما يرجع مستخدمهم

Serious condition
وبسي اتخد cephalo وحذرك من
ال allergy لازم اتخد skin test
اذا كان عندك

Adverse effects

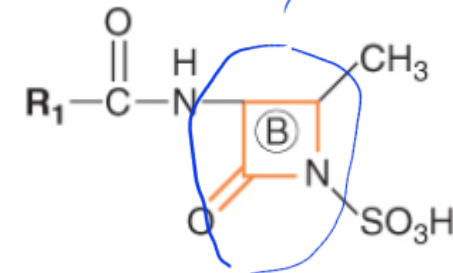
- ✓ pain after injection.
- ✓ Diarrhea.

لا تدمر البكتيريا
Normal flora

Some have anti-Vitamin K effect (bleeding).

Other B-Lactam Antibiotics- **Monobactams**

- They are drugs with a monocyclic β -lactam ring.
- Their spectrum of activity is limited to aerobic Gram-negative organisms (including *P aeruginosa*).
- **is resistant to the action of B-lactamases.**
- It is administered either IV or IM. Every 8 hrs
- this drug **may offer a safe** alternative for treating patients who are allergic to penic &/or cephalosporins.



Other B-Lactam Antibiotics- **Carbapenems**

- broad-spectrum B-lactam antibiotics.
- Examples: **Doripenem, Imipenem, Meropenem, Etrapenem.**
- They resist hydrolysis by most B-lactamases.
- Carbapenems are active against *P aeruginosa* and *Acinetobacter* species (except ertapenem).
- These agents have a very broad spectrum of action and are usually restricted to use in hospitals for treatment of serious infections.

→ empiric therapy • هو عبارة عن

Other B-Lactam Antibiotics- Carbapenems

- All are cleared renally, and the dose must be reduced in patients with renal insufficiency.
- Excessive levels of imipenem in patients with renal failure may lead to seizures.
- Imipenem undergoes cleavage by a **dehydropeptidase** found in the brush border of the proximal renal tubule. This enzyme **forms an inactive metabolite that is potentially nephrotoxic**.
 - Imipenem is formulated with cilastatin, which prevents hydrolysis of imipenem by renal dehydropeptidase.

anti-biotic

Combination
toxicity

طبيب
نفس
الكويت
Cilastatin
(Nephrotoxic)

Imipenem
إذا أخذته الشخص
nephrotoxicity
metabolism
dehydropeptidase
وهي التي تجعل
المه

Glycopeptide Antibiotics

- **Vancomycin** (MRSA / colitis)

Vancomycin inhibits synthesis of bacterial cell wall by binding to the D-Ala-D-Ala terminus preventing further crosslinking.

transpeptidase يمنع

- **IV** for systemic infections

بس ادا infection حاد
بنظرة ال oral انا عين
لاننا ما بنسجل الامتصاص
only

- Not absorbed after oral administration (the use of the oral formulation is limited to the treatment of severe antibiotic-associated C. difficile colitis.)

Narrow spectrum(G+ ve)

Bactericidal /not B-lactam.

VRE

طبقت
Resistant
من قبل
Staphylococcus
aureus

Gram (+) cocci

Staphylococcus aureus*
Staphylococcus epidermidis
Streptococcus groups A,B,C
Streptococcus pneumoniae
Enterococcus faecalis

*(including methicillin-resistant strains)

Gram (+) bacilli

Listeria monocytogenes
Corynebacterium jeikeium

Gram (-) cocci

Gram (-) rods

Anaerobic organisms

Clostridium species**

Spirochetes

Mycoplasma

Chlamydia

**Oral vancomycin only for C. difficile

Other

Actinomyces

Glycopeptide Antibiotics -

- **Vancomycin**
- **Orally:- every 6 hrs** for refractory pseudomembranous colitis due to *C. difficile*.
- **Slow IV infusion (1-2 hrs)** for treatment of systemic infections or prophylaxis.
 - is effective against MRSA. (DOC)
 - ~~Vancomycin~~ in combination with A.G alternative regimen to treatment of enterococcal endocarditis.
- **Teicoplanin** is a glycopeptide antibiotic that is very similar to vancomycin in mechanism of action and antibacterial spectrum.

Gram (+) cocci
Staphylococcus aureus* Staphylococcus epidermidis Streptococcus groups A,B,C Streptococcus pneumoniae Enterococcus faecalis *(including methicillin-resistant strains)
Gram (+) bacilli
Listeria monocytogenes Corynebacterium jeikeium
Gram (-) cocci Gram (-) rods
Anaerobic organisms
Clostridium species**
Spirochetes Mycoplasma Chlamydia
**Oral vancomycin only for <i>C. difficile</i>
Other
Actinomyces

Vancomycin

- S.E:-

- 1-Flushing (**red man syndrome**) with a **rapid** infusion. (**More common**)
- Prevented by prolonging the infusion period OR pretreatment with an antihistamine such as diphenhydramine.
- 2- phlebitis (inflammation of vein) at site of injection.
- 3- ototoxicity & nephrotoxicity (rare) but increased risk when administered with A.G.

بسبب المنطقة
حمرار في الرقبة والوجه
تسبب ال
histamine
Release

① Antihistamine يعطى قبل
② ببطء Slow Infusion

لـ يس اذا أخذاهم مع
A.G



Other Cell wall synthesis inhibitors

Fosfomycin:

UTI دوا؟

Inhibits the formation N -acetylmuramic acid precursor.

- **Therapeutic use** : It is indicated for urinary tract infections caused by E. coli or E. faecalis.
- Rapidly absorbed after oral administration & distributes well to the kidneys, bladder, and prostate

Bacitracin:

topical دوا
nephrotoxic
systemic دوا

Inhibits the carrier that transfers peptidoglycan subunits to the growing cell wall.

- It is highly nephrotoxic when administered systemically and is only used topically

Cell membrane active agents

لازم بهمين انت هدف
اي بيستقل cell membrane

- **Daptomycin** – is a new lipopeptide antibacterial drug.
- Binds to cell membrane causing depolarization and rapid cell death (doesn't work on cell wall).

بيستقل از phospholipids
by layer
منجز بها

- **Therapeutic use:**

- for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin resistant enterococci (VRE)
- is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus,

- **Adverse effect :**

Myopathy and creatine phosphokinase levels elevation.

monitoring
بصورت مستمر
لما يافى امره

اي بيستقل
Staphylococcus

other option
فان كان مستمرا لا اذات في

Questions??