بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 12

Antibiotics Pt.4

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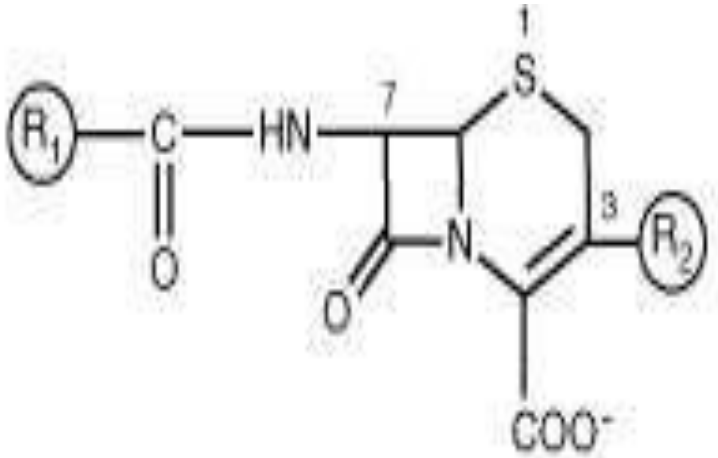
Cephalosporins

- Are also b-lactam antibiotics isolated from a strain of *Streptomyces*.
- There are a large number available for clinical use, variously termed "first- second- third- fourth generations.
- They are bactericidal and work in the same way as the penicillins.
- Resistance is due to b-lactamases, permeability mutants and mutations to the target proteins.

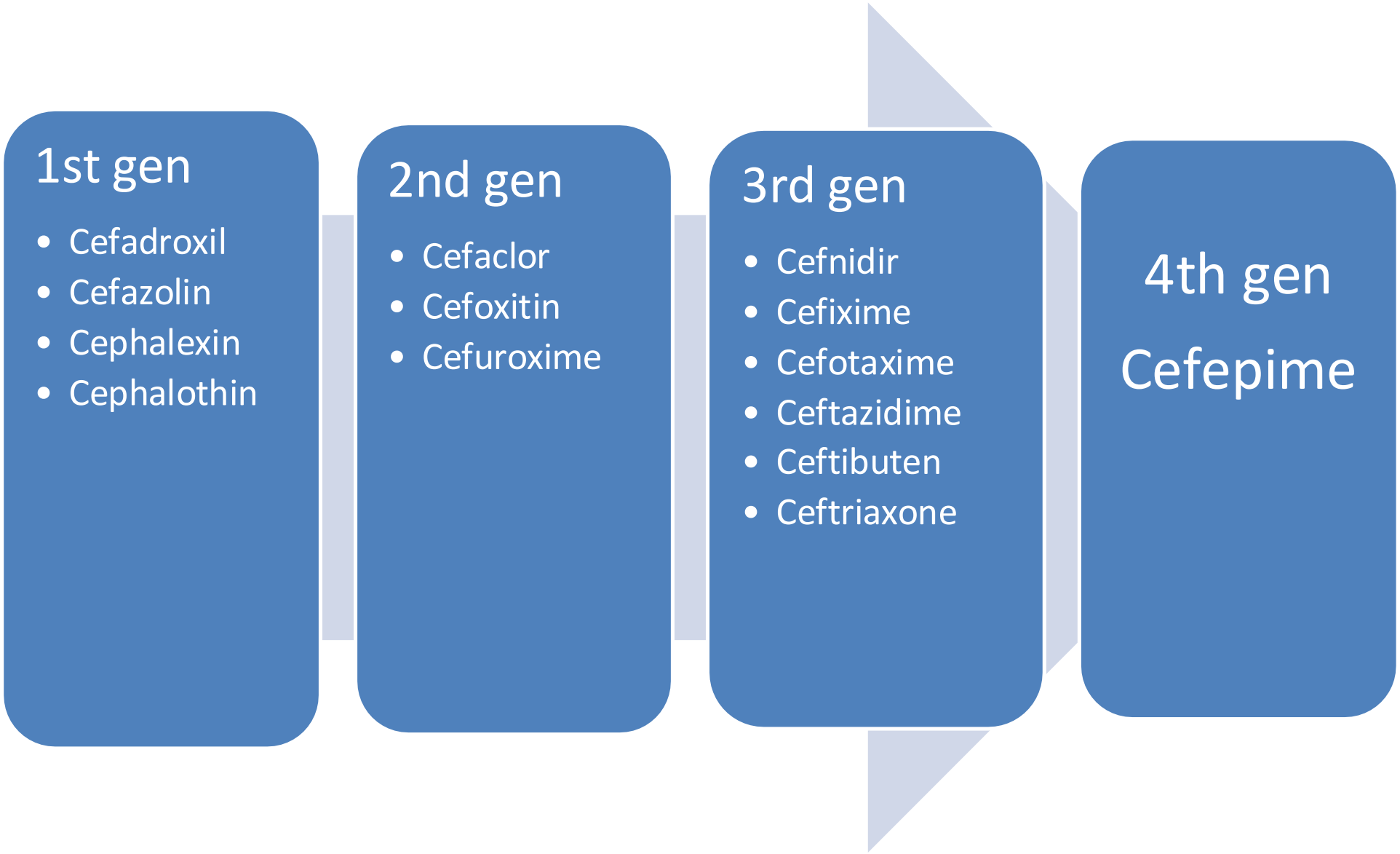
Cephalosporins

- **Bicyclic ring structure**
  - **beta-lactam ring (in common with penicillins)**
  - **6 membered sulfur containing dihidrothiaizine ring**

- **Changes in side chain R groups gives changes in spectrum of activity, pharmacokinetics, etc.**



Cephalosporins



Introduction to Cephalosporins:

Cephalosporins activity against **Gram-negative** bacteria increases as you move from the 1st to the 4th generation. These drugs are often used for the 10% of patients who are **hypersensitive to Penicillin**.

Note: No Cephalosporin (Generations 1-4) is active against Enterococcus.

1st Generation Cephalosporins:

These are "**Methicillin-like**" drugs used as alternatives for patients with Penicillin sensitivity. They are excellent against **Gram-positive** bacteria (**Staph** and **Strep**) commonly found on the **skin**, and not very active against gram negative bacteria.

Examples:

Cephalexin (Oral): This is the most common choice for skin and soft tissue infections, such as **cellulitis** in penicillin-hypersensitive patients. Other oral examples include **Cefadroxil and Cephalothin.**

Cefazolin (Injectable): This is used for **surgical prophylaxis** to prevent skin bacteria from causing infection during surgery. However, it is **not suitable** for abdominal surgeries (like colonectomy) because it **does not cover anaerobes like Bacteroides fragilis**, which live there.

Cephalosporins clinical uses

- **Some cephalosporins are given orally, eg. cephalexin, but most are administered intramuscularly or intravenously.**

- **Cephalosporins are second choice antibiotics for many infections including Gram-positive cocci such as *Staphylococcus, Streptococcus* and *Pneumococcus*, and Gram-positive rods such as *Clostridium*.**

- **They are first choice agents against Gram-negative rods of the *Enterobacteriaceae* such as *E. coli, Enterobacter* and *Klebsiella.***

1st generation Cephalosporins:

- **Act as penicillin G, but they are resistant to the staphylococcal penicillinase.**

  have good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms.

  Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus,* and *S. epidermidis*) are susceptible.

First Generation Cephalosporins

Best activity against gram-positive aerobes, with limited activity against a few gram-negative aerobes

Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group A/B/C/Gstreptococci

viridans streptococci

Gram-negative

E. coli

K. pneumoniae

P. mirabilis

- **The first-generation cephalosporins are excellent agents for skin and soft tissue infections owing to *S. aureus* and *S. pyogenes.***

- **A single dose of cefazolin just before surgery is the preferred prophylaxis for procedures in which skin flora are the likely pathogens .**

- **For colorectal surgery, where prophylaxis for intestinal anaerobes is desired, the second-generation agents cefoxitin or cefotetan are preferred.**

2nd Generation Cephalosporins:

Examples:

Cefuroxime (Zinnat) "Augmentin-like“:

This drug is active against **Staph**, **Strep**, **M.catarrhalis, H. influenzae, and Neisseria.** Because it kills the bacteria commonly found in these areas, it can be used **empirically** for **Upper Respiratory Tract infections**.

Cefoxitin & Cefotetan:

These are unique because they have additional activity against **anaerobes** like **Bacteroides fragilis**. Unlike the 1st generation, these drugs **are** effective for **abdominal surgeries** (like colonectomy) where anaerobes are present, making them the correct choice for prophylaxis in those procedures.

Cephalosporins generations

Second generation: have greater activity against three additional gram-negative organism : H influenzea, Neiseria, and Enterbactor erogenes. However, the activity against gram positive bacteria is weaker.

A subset of second-generation agents (*cefoxitin, cefotetan,* and *cefmetazole*) also is active against the *B. fragilis* group.

so can be used to treat mixed anaerobic infections such as peritonitis or diverticulitis.

Cefuroxime is used to treat community-acquired pneumonia because it is active against beta-lactamase-producing *H influenzae* or *K pneumoniae* and penicillin-resistant pneumococci.

Uses in Children:

Cefuroxime is often used for children who stay always at home. This is because it effectively treats common infections, such as **Streptococcus pneumoniae** and **Haemophilus influenzae**. While it covers those bugs, Cefuroxime does **not treat Mycoplasma,** which is acquired from school, universities.

Second Generation Cephalosporins
Spectrum of Activity

Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group A/B/C/G strep

viridans streptococci

Gram-negative

E. coli

K. pneumoniae

P. mirabilis

H. influenzae

M. catarrhalis

Neisseria sp.

Second Generation Cephalosporins
Spectrum of Activity

The cephamycins (cefoxitin and cefotetan) are the only 2nd generation cephalosporins that have activity against anaerobes

Anaerobes

Bacteroides fragilis

Bacteroides fragilis group

The 3rd Generation Cephalosporins:

3rd Generation Cephalosporins: Compared to previous generations, these have **increased activity against Gram-negative** bacteria and **decreased activity against Gram-positive** bacteria…

1. Ceftazidime:

- **Key Feature:** This is the **only** 3rd generation drug active against **Pseudomonas aeruginosa.**
- **Spectrum:** Active against all superbugs except MRSA
- It is considered **"Tazosyn-like"** (Tazosyn = Tazobactam + Piperacillin). If a patient is sensitive to **Tazosyn**, we will give him **Ceftazidime** as an alternative.

2. Ceftriaxone:

- **Primary Use:** Used to treat **meningitis** because it crosses the **blood-brain barrier (BBB)** well.
- **Spectrum:** Covers most Gram-positive and Gram-negative bacteria, **except Pseudomonas aeruginosa.**
- **Note (Important):** Do **not** use in children **under 42** weeks who have **jaundice (hyperbilirubinemia),** because it might cause bilirubin to precipitate causing death. So we will use **Cefotaxime as an alternative** for these children.

3. Cefdinir & Cefixime:

- **Route:** Oral drugs.
- **Target:** Active against E. coli (which is very common in Jordan).

Third-generation cephalosporins

- **generally are less active than first-generation agents against gram-positive cocci, but more active on gram negatives.**
- **but they are much more active against the Enterobacteriaceae, including beta-lactamase-producing strains.**
- **A subset of third-generation agents (*ceftazidime* and *cefoperazone*) also is active against *P. aeruginosa.***

Clinical uses

- **The third-generation cephalosporins, with or without aminoglycosides, have been considered to be the drugs of choice for serious infections caused by *Klebsiella, Enterobacter, Proteus, Serratia,* and *Haemophilus* spp (superbugs).**

- **They may be particularly useful in treating hospital-acquired infections.**

  although increasing levels of extended-spectrum beta-lactamases are reducing the clinical utility of this class of antibiotics.

Clinical uses

- **In neutropenic, febrile immun-ocompromised patients, third-generation cephalosporins are often used in combination with an aminoglycoside (for people taking anti-cancer drugs).**

- **Other potential indications include empirical therapy of sepsis of unknown cause in both the immunocompetent and the immunocompromised patient**

Third Generation Cephalosporins
Spectrum of Activity

Gram-negative aerobes

E. coli, *K. pneumoniae*, *P. mirabilis*

H. influenzae, *M. catarrhalis*, *N. gonorrhoeae* (including beta-lactamase producing); *N. meningitidis*

Citrobacter sp., *Enterobacter* sp., *Acinetobacter* sp.

Morganella morganii, *Serratia marcescens*, *Providencia*

Pseudomonas aeruginosa (ceftazidime and cefoperazone)

Clinical uses

- **Ceftriaxone and cefotaxime**

1. **are used for the initial treatment of meningitis in nonimmunocompromised (in combination with vancomycin)**

   because of their antimicrobial activity, good penetration into CSF, and record of clinical success.

2. **are the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains.**

3. **Ceftriaxone is the therapy of choice for all forms of gonorrhea and for severe forms of Lyme disease.**

The 4th generation cephalosporins:

4th Generation Cephalosporins (Cefepime/Cefamax):

Spectrum: Active against most Gram-positive and Gram-negative bacteria, but **inactive against MRSA**, because MRSA has a changed binding proteins, so antibiotics can't bind to it to kill it.

NOTE: Unlike 3rd generation drugs, **Cefepime does not induce ESBL** (Extended Spectrum Beta-Lactamases).
What is ESBL? Enzymes produced by bacteria that break down antibiotics, making the bacteria more resistant to antibiotics. So Cefepime can kill bacteria that produce ESBL enzyme.

- **Usage:**
- Because it doesn't induce resistance, we save Cefepime for specific situations.
- We can use **Cefepime** for bacteria (like E. coli) that **produce ESBL and are resistant to 3rd generation cephalosporins.**

Additional Resources:

رسالة من الفريق العلمي:

اذكرونا بدعوة صادقة بظهر الغيب.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			