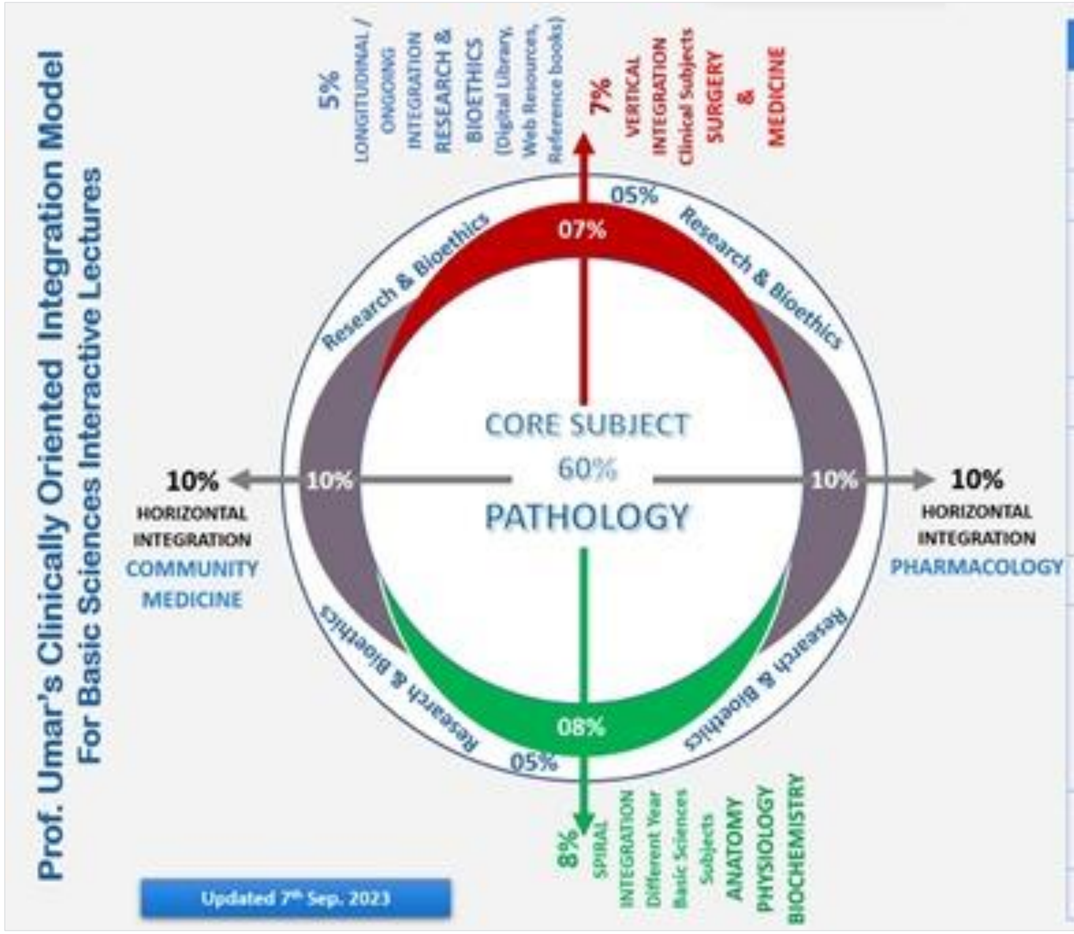
CEPHALOSPORINS

Dr. Zunera Hakim

SOURCES:

- **BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION**
- **GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION**

UMAR'S MODEL OF INTEGRATION



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

LEARNING OBJECTIVES

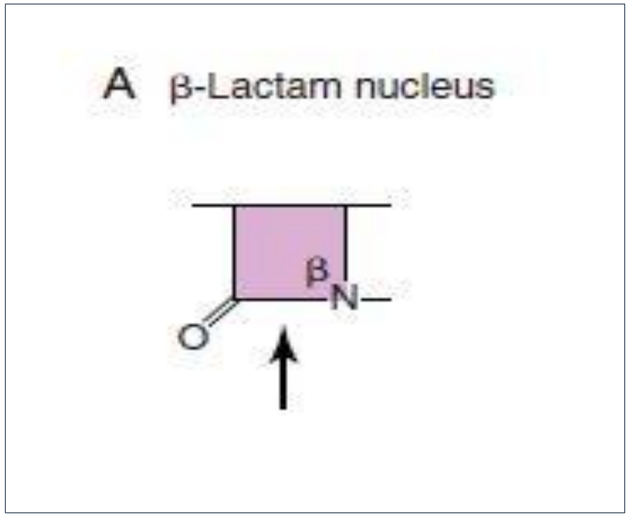
At the end of this LGIS, students of 3rd Year MBBS should be able to;

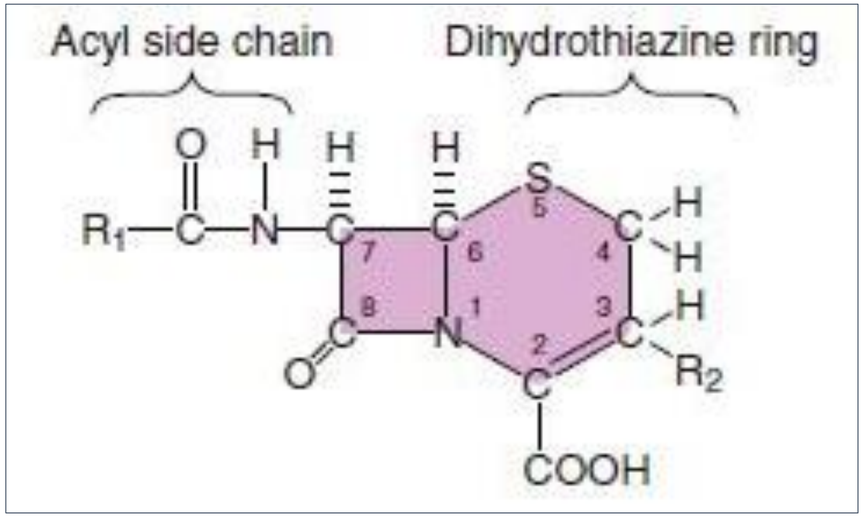
- Identify the source and chemistry of cephalosporins
- Classify cephalosporins & recognize the basis of classification
- Describe salient pharmacokinetic properties of various cephalosporins
- Recall the MOA of beta lactam anti-microbials
- Recognize the spectrum of activity & correlate the clinical uses of different classes of cephalosporins
- Describe the adverse effects of cephalosporins

History & source

- Brotzu (1945) isolated a mold ***Acremonium chrysogenum*** in sewer water of coast of Sardinia
- Culture fluids in which the Sardinian fungus was cultivated were found to contain three distinct antibiotics, which were named *cephalosporin P, N,* and *C*.
- First introduced into clinical use in 1964 (cephalothin)

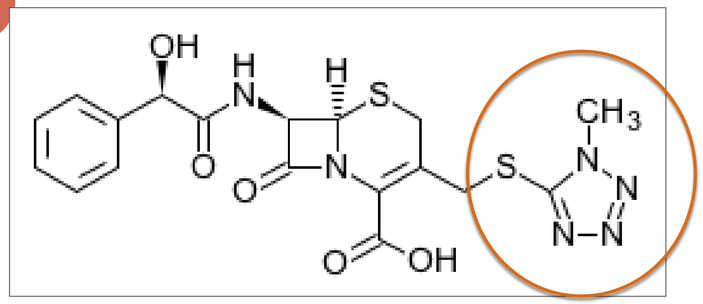
Chemistry



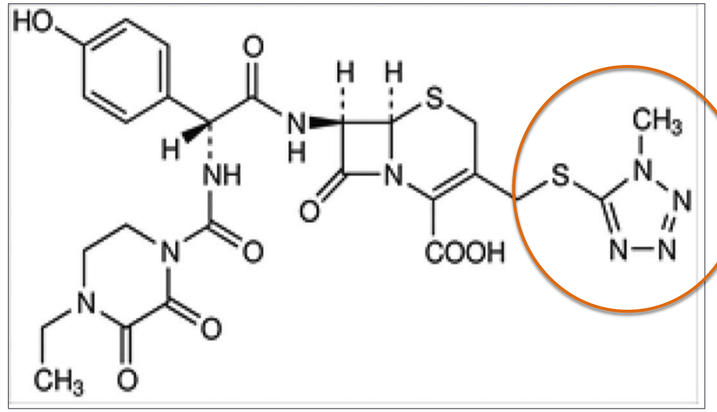


- Derivatives of 7-aminocephalosporanic acid
- Water soluble; stable to pH & temperature changes
- More stable than penicillin
- **Cephamycins:** methoxy group at position7
- **Oxycephems:** sulfur replaced by oxygen at R1
- **Carbacephems:** sulfur replaced by carbon atom at R1

Chemistry



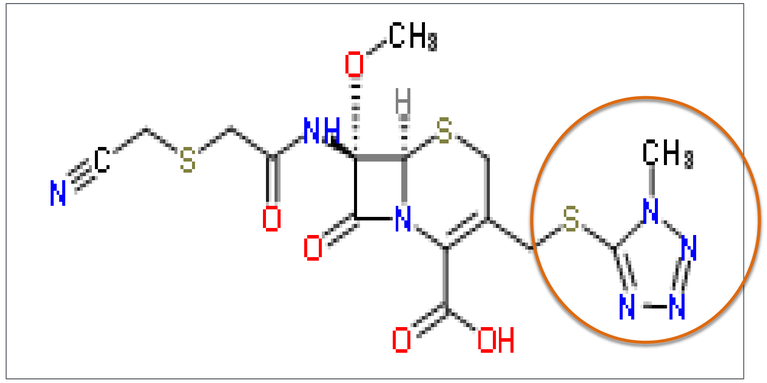
Cefamandole



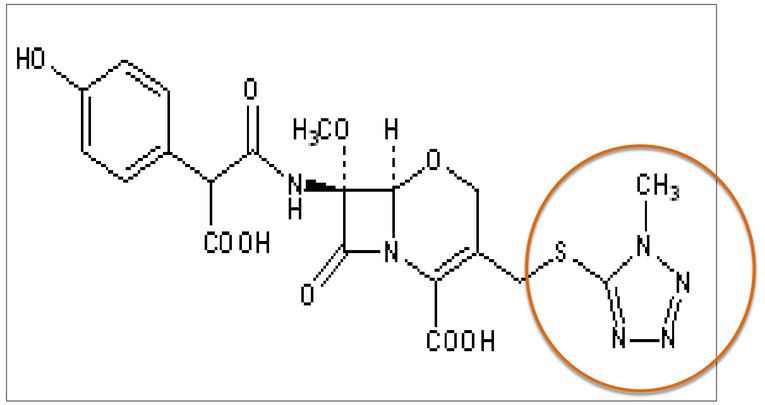
Cefoperazone

N-methylthiotetrazole

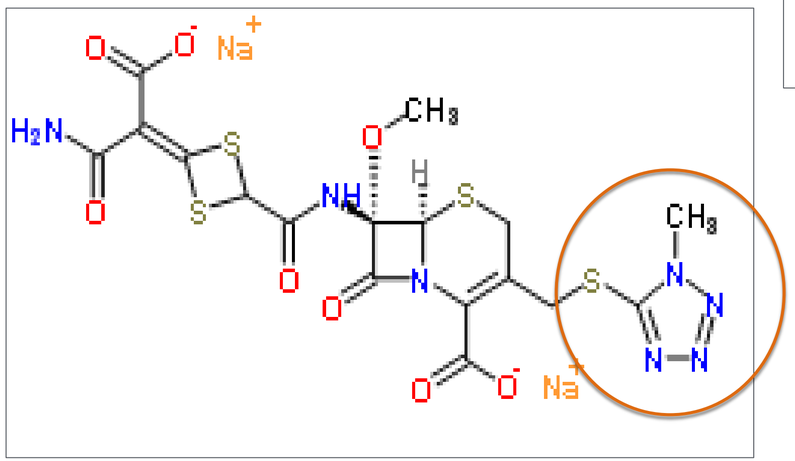
(MTT) substitution



Cefmetazole

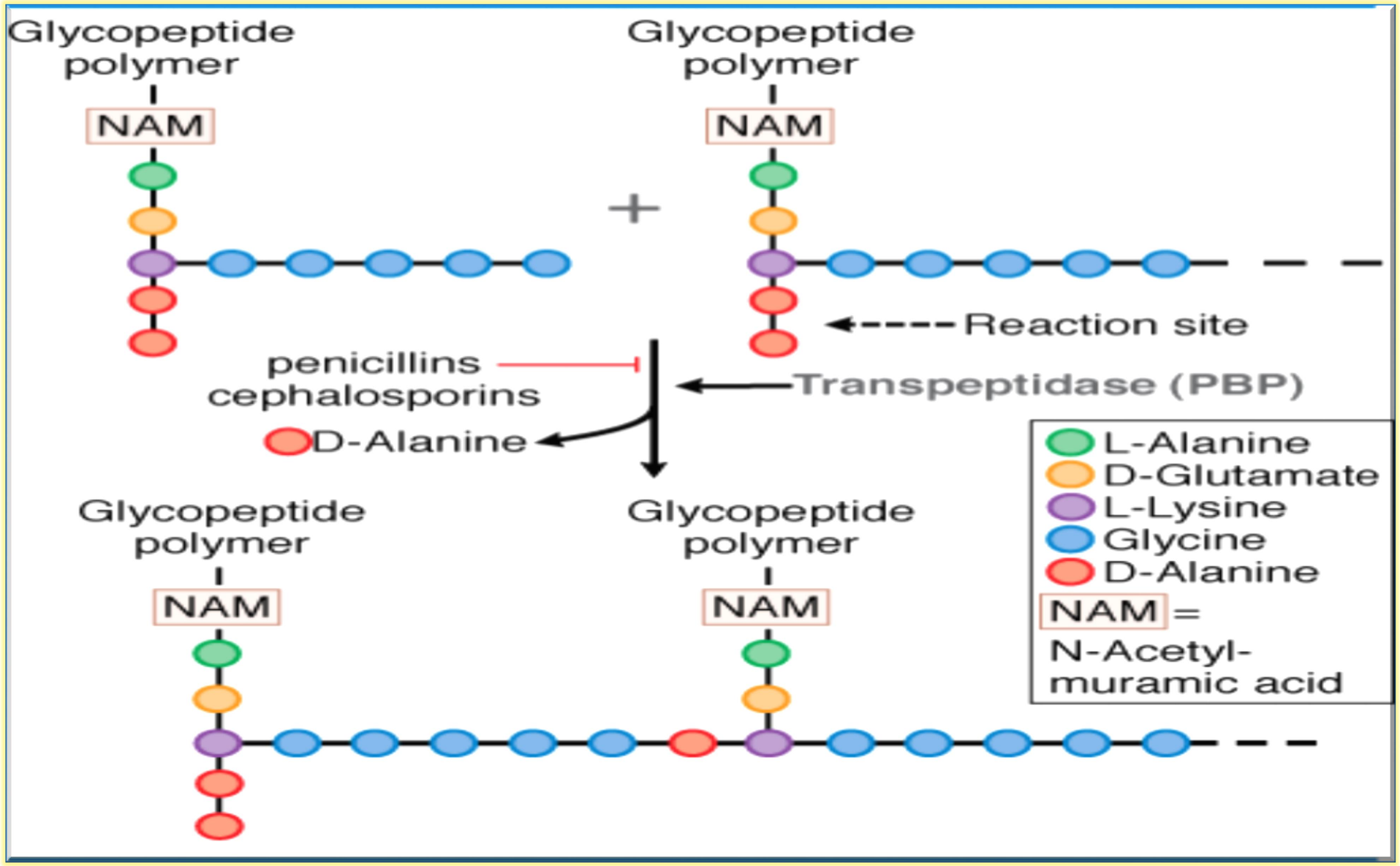


Moxolactam



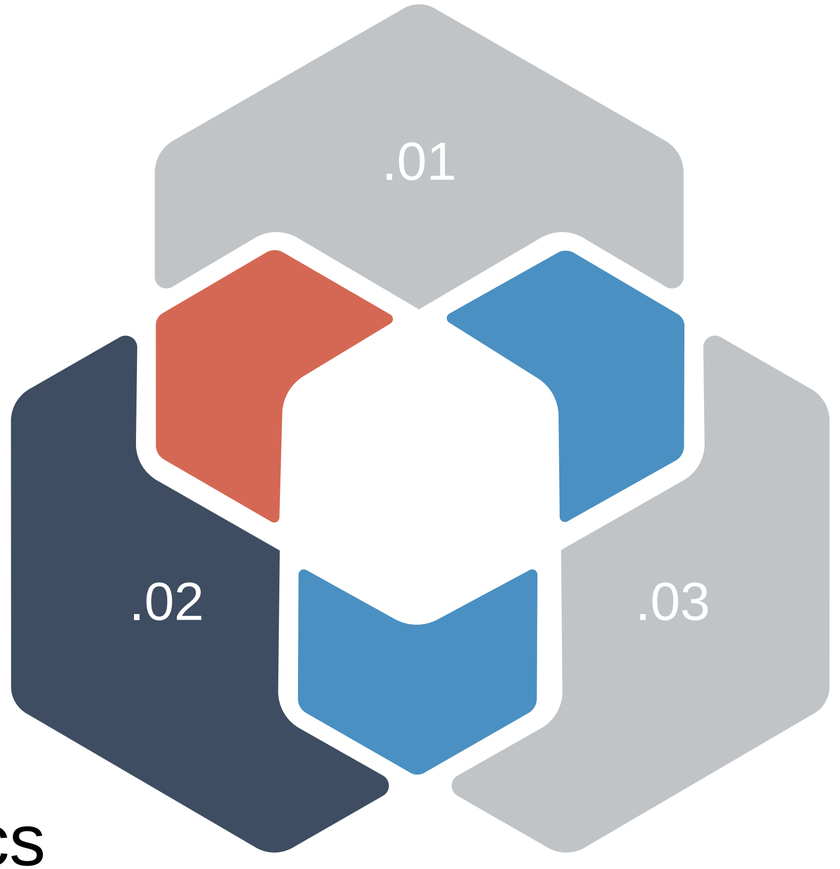
Cefotetan

Mechanism of Action



Resistance

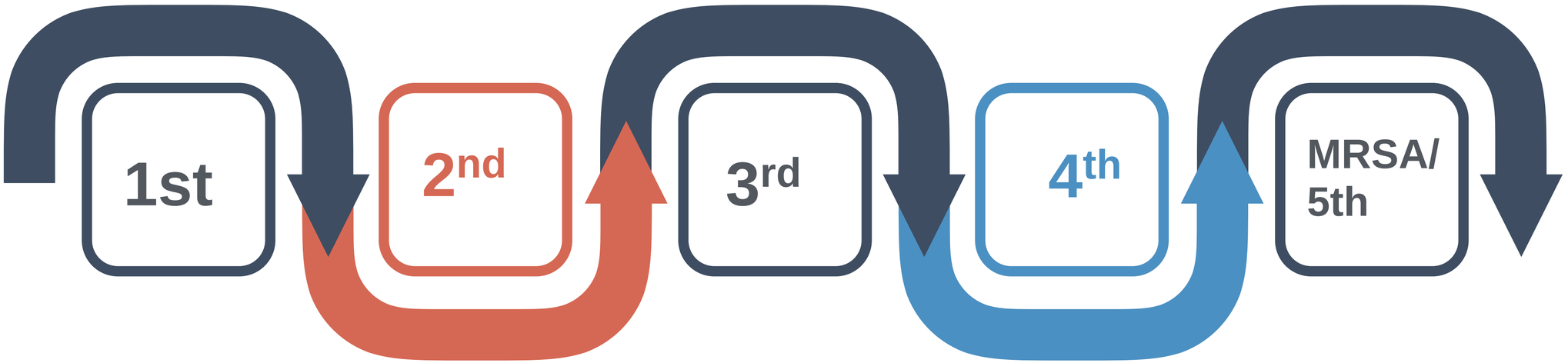
- Destruction by β-lactamases
- Failure to reach the target PBPs
  - Decrease permeability of cell wall
  - Efflux pumps (*Pseudomonas aeruginosa)*
- Modification of target PBPs
  (two PBP 1A and 2X)



Cross-resistance

- Resistance to other β Lactam antibiotics

Generations



Activity against Gram Negative

Resistance to destruction by β lactamases

Penetration into CNS

.01

First generation

Spectrum

- Gram +tive *(MSSA, Streptococci)* (good activity)
- Gram –tive (moderate activity) *E. coli, P. mirabilis, & K. pneumoniae*
- Anaerobic cocci (*peptococci, peptostreptococci*) are sensitive

Parenteral

- Cephalothin
- **Cefazolin (IV/IM)**
- Cephradine
- Cephaloridine
- Cephapirin

Oral

- Cefadroxil
- Cephalexin
- Cephradine
- Cephaloglycin

.02

Second generation

Spectrum

- Gram +tive including those resistant to 1st generation
- Gram –tive (increasing activity)
- *H.influenzae, Klebseilla & proteus*
- *B.fragilis (cefoxitin,cefotetan & cefmetazole)*

Parenteral

- Cefuroxime
- Cefamandole
- Cefonicid
- Ceforanide
- Cefprozil
- Cefoxitin
- Cefotetan
- Cefmetazole

Cephamycin

Oral

- Cefuroxime axetil
- Cefaclor
- Cefprozil
- Loracarbef

.03

Third generation

Spectrum

- Gram –tive (*citobacter, acinetobacter,* ***enterobacter,*** *providencia, serratia,E.coli, H.influenza,*
- *Klebsiella, Neiserria)*
- *Pseudomonas* (ceftazidime,ceftolozane & cefoperazone)
- Less active than 1st generation against gram +tive

Parenteral

- Ceftriaxone
- Cefotaxime
- Ceftizoxime
- Ceftazidime
- Cefoperazone
- **Ceftolozane**

Oral

- Cefixime
- Cefdinir
- Cefditoren pivoxil
- Ceftibuten
- Cefpodoxime proxetil

.04

Fourth generation

Spectrum
(Expanded)

- Gram +tive &–tive
  (*Pseudomonas,*
  E.coli, Klebsiella,
  Proteus, H.influenzae, Neiserria
  Enterobacter, B.fragilis,
  Streptococci pyogenes & MSSA)

Spectrum same but differ in resistance to β lactamases

Parenteral

- Cefepime
- Cefpirome

.05

MRSA active cephalosporins

can be called
Fifth generation

Spectrum
(Expanded)

- MRSA,VRSA, penicillin resistant *S.pneumoniae*
- Gram –tive
  (*H.influenzae,*
  Moraxella catarrhalis)

Parenteral

- Ceftaroline fosamil
- Ceftobiprole medocaril

Siderophore cephalosporin

Spectrum

- Drug resistant gram –tive (*Enterobacteriaceae, Pseudomonas,Acinetobacter)*

Parenteral

- Cefiderocol

Cephalosporins plus β lactamase inhibitors

- Ceftazidime and avibactam (4 : 1 ratio)
- Ceftaroline and avibactam (1 : 1 ratio)
- Ceftolozane and tazobactam (2 : 1 ratio)

- Active against gram-negative organisms, (*P aeruginosa* & AmpC & extended-spectrum β-lactamase producing Enterobacteriaceae.

- Complicated intra-abdominal infections and urinary tract infections

Antipseudomonal cephalosporin

- Ceftazidime
- Ceftazidime plus avibactam
- Cefipime
- Cefpirome
- Ceftolozane plus tazobactam

Organisms resistant to Cephalosporins

- ***L****isteria monocytogenes*
- ***E****nterococcus faecalis*
- ***E****nterococcus faecium*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Legionella micdadei*
- *C. Difficile*
- *Campylobacter jejuni*;

Pharmacokinetics

- Oral and parenteral preparations available within 1st,2nd & 3rd generations.
- The prodrugs cefuroxime axetil & cefpodoxime proxetil are oral formulations in which the ester is hydrolyzed in intestinal mucosa
- Widely distributed (bone, soft tissue, muscle, pericardial & synovial fluids); a few crosses BBB to reach therapeutic concentrations in CSF (3rd & 4th generation)
- Cefotaxime is deacetylated to active metabolite
- Half life is around 1-4hrs exception ceftriaxone with t1/2 of 8hrs
- Mostly renally excreted (tubular secretion), cefoxitin, cefotetan, ceftriaxone,cefoperazone with significant biliary excretion

TABLE 46–3 Pharmacokinetic Parameters of Cephalosporins

Cephalosporin	Route of Administration	Half-Life (hrs)	Protein Bound (%)	Route of Elimination	CSF Penetration*
First Generation					
Cefazolin	IV/IM	2.0	85	R	
Cephalexin	Oral	1.0	15	R	
Cefadroxil	Oral	1.5	20	R	
Second Generation					
Cefaclor	Oral	1.0	25	R, M	
Cefprozil	Oral	1	20	R	
Loracarbef	Oral	1	25	R	
Cefuroxime	IV/IM/Oral	1.7	35	R	Yes
Cefoxitin	IV/IM	0.8	70	R	
Cefotetan	IV/IM	3.5	85	R	
Cefprozil	Oral	1.3	45	R	
Third Generation					
Cefotaxime	IV/IM	1.0	50	R	Yes
Ceftizoxime	IV/IM	1.8	30	R	Yes
Ceftriaxone	IV/IM	6-8	90	R(50%), B(60%)	Yes
Cefixime	Oral	3.7	75	R(50%), (other)	
Ceftazidime	IV/IM	1.8	15	R	Yes
Cefpodoxime	Oral	1.2	25	R	
Fourth Generation					
Cefepime	IV/IM	2.1	20	R	Yes

Therapeutic Uses

1st Generation

- **Surgical prophylaxis** e-g cardiac & orthopedic prosthesis procedures (cefazolin)
- **Skin & soft tissue infections**(cellulitis & abscess)
- **Respiratory tract infections** (*streptococcal* pharyngitis)
- Alternative to **antistaphylococcal penicillins** in case of allergy

Therapeutic Uses

2nd Generation

- **Sinusitis, otitis media & bronchitis** caused by *H influenza, Moraxella catarrhalis* **(loracarbef,cefaclor)**
- **Community acquired pneumonia** by Beta lactamase producing *H. influenzae or K pneumoniae &* penicillin resistant *Pneumococci* **(cefuroxime)**
- **Mixed aerobic & anaerobic infections** (peritonitis & diverticulitis, PID) **(cefoxitin & cefotetan)**
- **Perioperative prophylaxis** for intra-abdominal & gynecological surgical procedures **(cefoxitin & cefotetan)**

Therapeutic Uses

3rd Generation

- **Meningitis** caused by *H. influenzae, N. meningitidis* , *S. pneumoniae* ***(ceftriaxone, cefotaxime)***
- **Community acquired pneumonia**caused by penicillin resistant pneumococci ***(ceftriaxone, cefotaxime)***
- **Gonococcal infection,** resistant to penicillin & quinolone **(ceftriaxone with azithromycin, cefixime)**
- **Bacterial septicemia/febrile neutropenia** (empirical therapy in immunocompetent & immunocomprosmised pateints) **(ceftazidime)**
- **Enteric fever** not responding to other therapy. **(cefoperazone , ceftriaxone)**

Therapeutic Uses

3rd Generation

- **Nosocomial infections** caused by susceptible organisms **(ceftriaxone & cefotaxime)**
- **Respiratory infections** such as otitis media, sinusitis, & acute exacerbations of chronic bronchitis**(cefdinir, cefixime,ceftibuten, cefditoren pivoxil & cefpodoxime proxetil**)
- **Lyme's disease** (CNS or joint involvement) **(ceftriaxone & cefotaxime)**
- **Skin/soft tissue & bone/joint infections**
- **UTI (complicated & uncomplicated)**
- **Nonenterococcal streptococcal endocarditis (ceftriaxone)**

Therapeutic Uses

3rd Generation

- **Chancroid & penicillin allergic patients of syphilis (ceftriaxone)**
- **Eradication of nasopharyngeal carriage of** *N. meningitidis* **(ceftriaxone)**
- **Pseudomonal infections (ceftazidime & cefoperazone)**

Therapeutic Uses

4th Generation

- **Empiric therapy** for febrile neutropenic patients
- **Pneumonia** (moderate to severe) caused by *Streptococcus pneumoniae, Pseudomonas aeruginosa* , *Klebsiella pneumoniae*, or *Enterobacter* species
- **Uncomplicated and complicated UTIs** (including pyelonephritis) caused by *Escherichia coli* , *Klebsiella pneumoniae* , or *Proteus mirabilis*

Therapeutic Uses

4th Generation

- **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*
- **Complicated intra-abdominal infections** (in combination with metronidazole) caused by *Escherichia coli*, streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* species, or *Bacteroides fragilis*

Adverse effects

Hypersensitivity

Cross reactivity with penicillin is low (1%)

- Anaphylaxis, skin rashes, fever, nephritis, granulocytopenia & hemolytic anemia

GIT

Diarrhea

- Biliary pseudolithiasis (CEFTRIAXONE)

Superinfection

Pseudomembranous colitis *(Clostridium difficile)*

Methylthiotetrazole group

Cefamandole,cetmetazole,cefoperazone, cefotetan

- Disulfiram reaction
- Bleeding, hypoprothrombinemia & coagulation abnormalities (Vit K)

Toxicity

- Pain after IM, thrombophelibiltis after IV
- Renal toxicity (interstitial nephritis & tubular necrosis)
- Hematological (eosinophilia,cytopenia)
- CNS toxicity (encephalopathy & nonconvulsive status epilepticus)

RESEARCH

Jorda A, Zeitlinger M. Pharmacological and clinical profile of cefiderocol, a siderophore cephalosporin against gram-negative pathogens. Expert Review of Clinical Pharmacology. 2021 Jul 3;14(7):777-91.

BIOETHICS

Despite the availability of new Food and Drug Administration-approved antibiotics, clinicians continue to frequently prescribe older antibiotics with suboptimal safety-efficacy profiles for the treatment of resistant gram-negative infections.

> “[P]rimary prescribers in hospitals may be less aware about recently approved antibiotic options as compared with infectious disease specialists and pharmacists.”

Investigators affiliated with the National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative conducted a retrospective cohort study to understand use patterns of 7 gram-negative antibiotics that have had FDA approval since 2014. The study included administrative claims data captured across 619 hospitals between January 2016 and June 2021. The approved gram-negative antibiotics were ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, plazomicin, eravacycline, imipenem-relebactam-cilastatin, and cefiderocol.

ARTIFICIAL INTELLIGENCE

Oselusi SO, Fadaka AO, Wyckoff GJ, Egieyeh SA. Computational target-based screening of anti-MRSA natural products reveals potential multitarget mechanisms of action through peptidoglycan synthesis proteins. ACS omega. 2022 Oct 14;7(42):37896-906.

END OF LECTURE ASSESSMENT

A patient’s history notes a documented severe reaction to a penicillin. What other antibiotic or class is likely to cross-react and so should be avoided in this patient?

a. Aminoglycosides
b. Azithromycin
c. Cephalosporins
d. Erythromycin
e. Linezolid

END OF LECTURE ASSESSMENT

Compared with most other cephalosporins, the administration of cefmetazole, cefoperazone, or cefotetan is associated with a higher incidence of an adverse response that is particularly dangerous for some patients. What is that rather unique adverse response?

a. Acute heart failure
b. Acute renal failure
c. Bleeding tendencies in patients taking warfarin
d. Hypertension
e. Ototoxicity