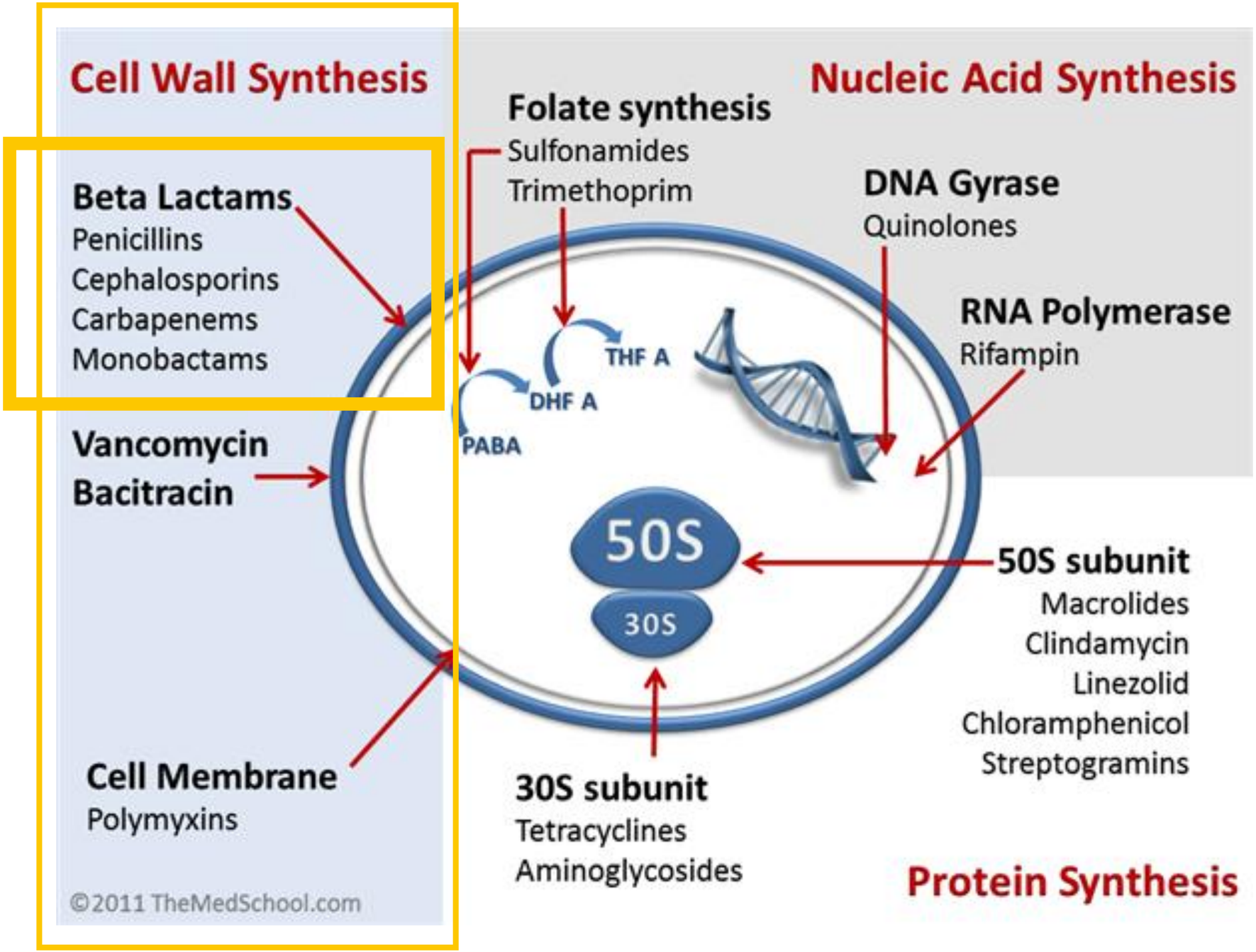
THE DEVELOPMENT OF BETA-LACTAM ANTIBIOTICS

Basic science Infectious

R2 Teeragarn


Cell Wall Synthesis
Beta Lactams
Penicillins
Cephalosporins
Carbapenems
Monobactams
Vancomycin
Bacitracin
Cell Membrane
Polymyxins
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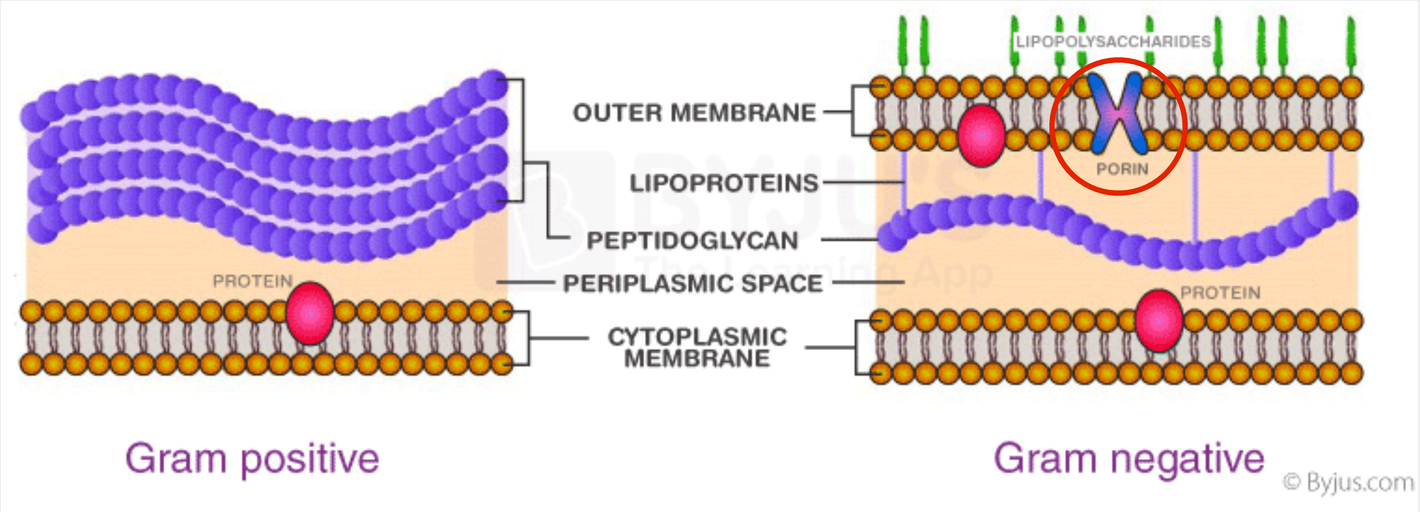
Folate synthesis
Sulfonamides
Trimethoprim
Nucleic Acid Synthesis
DNA Gyrase
Quinolones
RNA Polymerase
Rifampin
THF A
DHF A
PABA
50S
30S
50S subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol
Streptogramins
30S subunit
Tetracyclines
Aminoglycosides
Protein Synthesis

Outline

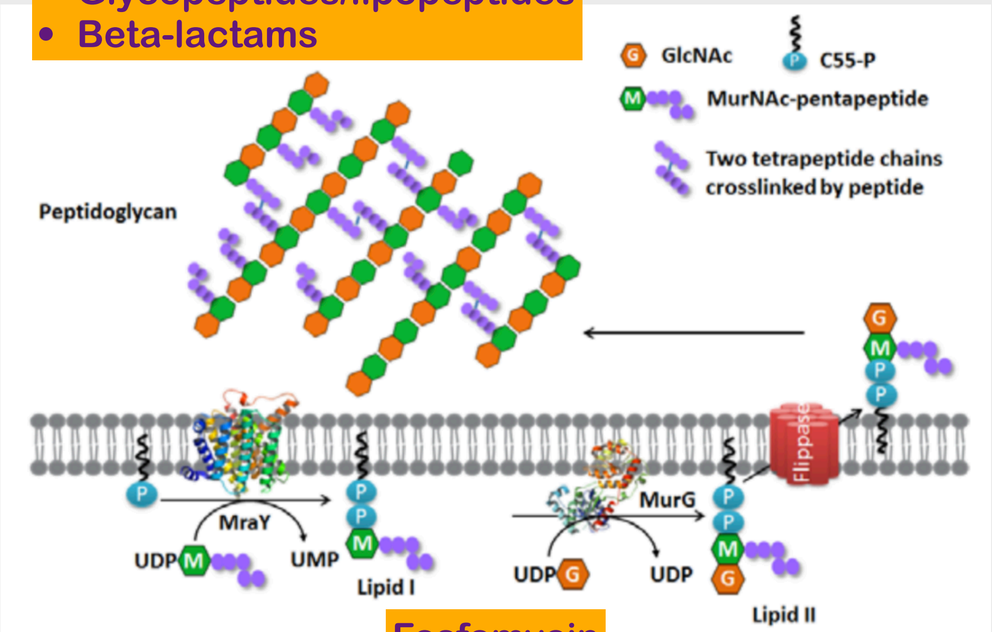
- Bacterial Cell Wall
- Beta-lactam Mechanism of action
- Penicillins
- Cephalosporins

Bacterial Cell Wall

- Structural strength and Protective barrier for the bacterium
- The peptidoglycan layer is composed of
  - polysaccharides : N-acetylglucosamine, N-acetylmuramic acid
  - 3 and 5 amino acids : typically pentapeptide



- Glycopeptides/lipopeptides
- Beta-lactams



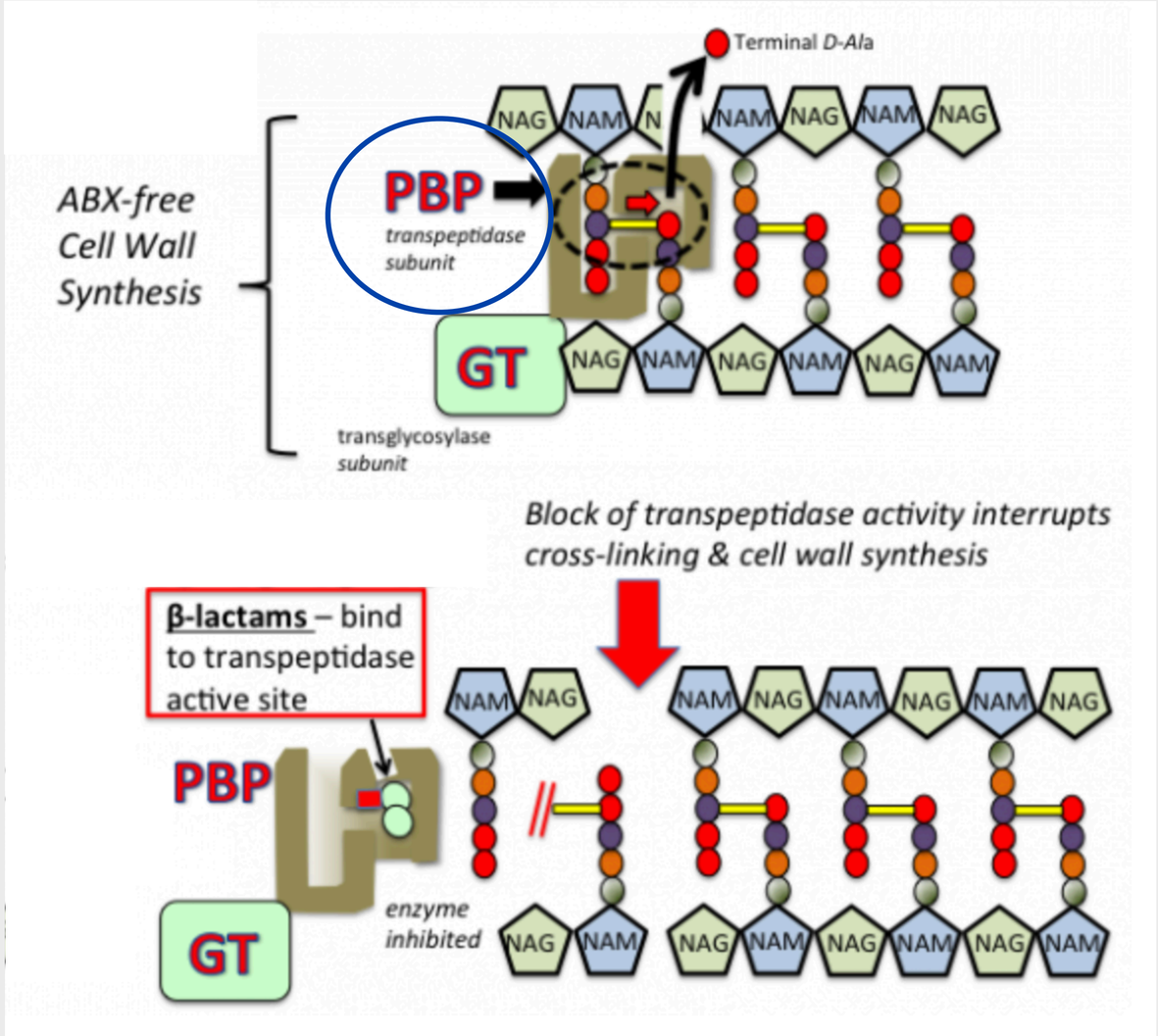
Fosfomycin

The Membrane Steps of Bacterial Cell Wall Synthesis as Antibiotic Targets, Antibiotics (Basel). 2016 Sep; 5(3): 28.

Beta-lactam Mechanism of action

Penicillin-binding proteins : PBPs

- PBPs = Cross-link of peptidoglycan
- Beta-lactam ring interact PBPs
  - -> disruption of peptidoglycan layer
  - -> bacterial lysis

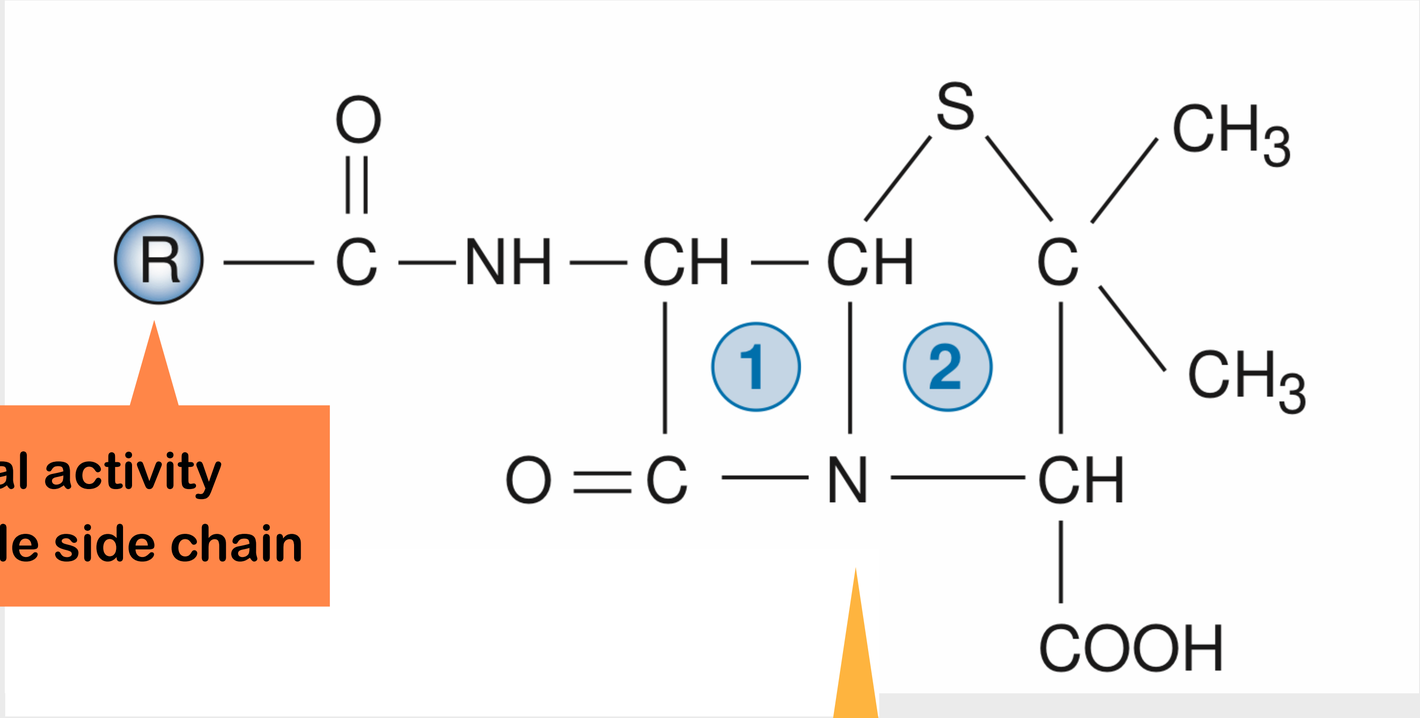


NAG: N-acetylglucosamine, NAM: N-acetylmuramic acid

The Membrane Steps of Bacterial Cell Wall Synthesis as Antibiotic Targets, Antibiotics (Basel). 2016 Sep; 5(3): 28.

Penicillins

Penicillins



Antibacterial activity

R : Variable side chain

Altered pharmacologic properties

1. **Beta-lactam ring**
2. **Thiazolidine ring**

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

Penicillins

1. Natural penicillins
2. Penicillinase-resistant penicillins
3. Aminopenicillins
4. Extended-spectrum penicillins
5. β-lactam plus β-lactamase inhibitors

1 Natural Penicillins

Penicillin G, Penicillin V

- Purified directly from cultures of Penicillium mold

Gram-positive	Streptococcus pyogenes Viridans group streptococci Streptococcus pneumoniae
Gram-negative	Neisseria meningitidis Haemophilus influenza *
Anaerobe	Clostridia spp. (except C. difficile)
Spirochetes	Treponema pallidum Leptospira spp.

* Non-Beta-lactamase producing pathogen

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

1 Natural Penicillins

- Benzylpenicillin : 4 salt forms
  Penicillin G sodium, potassium, benzathine, procaine

Penicillin G Sodium

- IV form
- rapid onset 30 min
- short half-life of 30-60 min

1. Leptospirosis
2. Congenital syphilis
3. Toxic shock syndrome

Penicillin G benzathine

- IM form
- slower absorption and longer duration of action

1. Secondary prophylaxis for rheumatic heart disease
2. Syphilis

Penicillin V

- oral form
- stable in gastric secretion
- relatively low peak plasma levels

1. Secondary prophylaxis for rheumatic heart disease
2. Mild infection

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

2 Penicillinase-resistant penicillins

Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin

- Penicillinase = 1st beta-lactamase
- Prevents penicillinase produced by Staphylococcus
- Methicillin = prototype ATB
- Unable to bind PBPs of MRSA

Gram-positive	Staphylococcus aureus

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

3 Aminopenicillins

Ampicillin, Amoxicillin

- Adding an amino group to the benzylpenicillin molecule
- Side chain increases hydrophilicity --> pass through the porins of some enteric gram-negative rods

Gram-positive	Streptococci Enterococci Listeria monocytogenes
Gram-negative	Neisseria meningitidis Haemophilus influenza * Enterobacteriaceae *

* Non-Beta-lactamase producing pathogen

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

3 Aminopenicillins

Ampicillin

- IV and Oral form
- optimally dosed at least every 6 hr

Amoxicillin

- Oral form
- longer half-life
- higher serum concentration
- administered every 8 hr

Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

4 Extended-spectrum penicillin

Piperacillin

- Greater penetration into gram-negative bacteria
- More resistant to cleavage by gram-negative β-lactamases

Gram-positive	Streptococci Enterococci
Gram-negative	N. meningitidis H. influenza Enterobacteriaceae Pseudomonas aeruginosa
Anaerobe	Clostridia spp. (except C. difficile) Bacteroides spp. *

* Non-Beta-lactamase producing pathogen

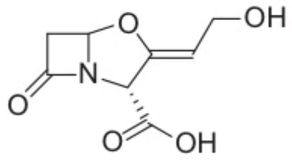
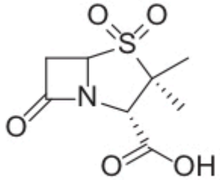
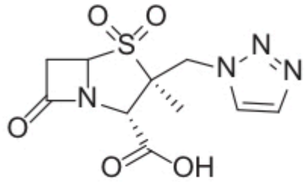
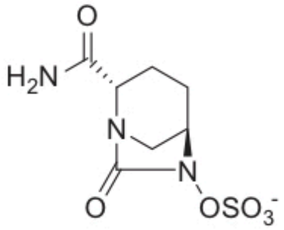
Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

Beta-lactamase inhibitors

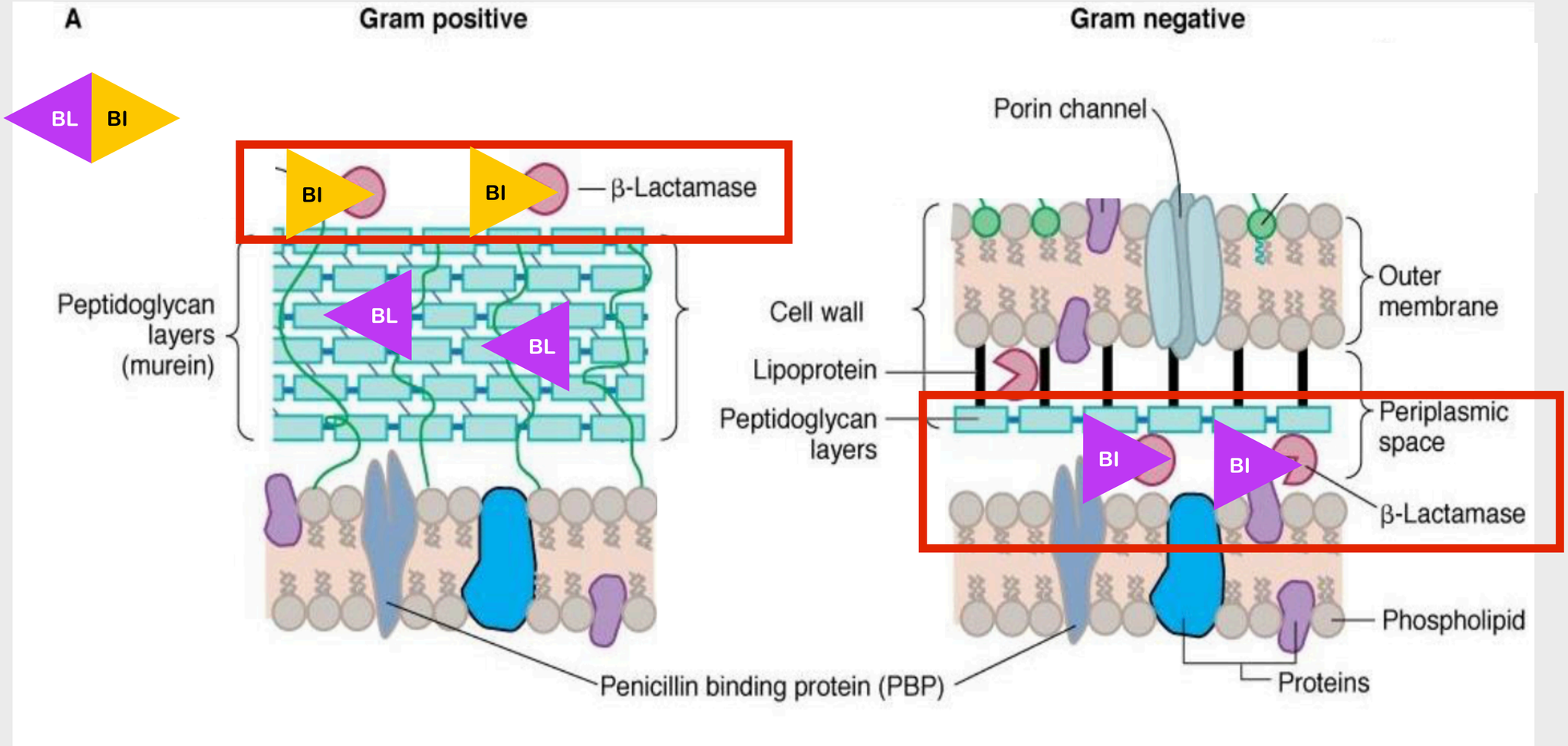
Clavulanic acid, Sulbactam, Tazobactam

- Structurally similar to penicillin
- Bind Beta-lactamases --> preventing its attack on the beta-lactam ring
- No intrinsic antimicrobial activity <u>except</u> sulbactam

Table 6. β-lactamase inhibitors of current interest

Name	Structure	Subclass	Partner β-lactam
Clavulanic acid[b]		Clavam	Amoxicillin
Sulbactam[c]		Penicillanic acid sulfone	Ampicillin
Tazobactam		Penicillanic acid sulfone	Piperacillin Ceftolozane
Avibactam[d]		DBO[e]	Ceftazidime[d]

Beta-lactamase inhibitors



5 Beta-lactam plus Beta-lactamase inhibitors

	Ampicillin-sulbactam Amoxicillin-clavulanate	Piperacillin-tazobactam
Gram-positive	Staphylococcus aureus same as ampicillin	Staphylococcus aureus same as piperacillin
Gram-negative	H. influenza Enterobacteriaceae ESBL	Enterobacteriaceae ESBL ** Pseudomonas aeruginosa **
Anaerobe	Clostridia spp. (except C. difficile) Bacteroides spp.	Clostridia spp. (except C. difficile) Bacteroides spp.

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5 Beta-lactam plus Beta-lactamase inhibitors

Amoxicillin-clavulanate

Skin & soft tissue infection
Respiratory tract infection : AOM, pneumonia, sinusitis

Preparation	Amoxicillin/clavulanate (mg)	Interval
4:1	500/125 (tab)	
7:1 (228 mg/5 ml) (457 mg/5 ml)	200/28.5 400/57	tid
14:1 (642.9 mg/5 ml)	600/42.9 (high dose amoxicillin)	bid

S. aureus

Penicillinase

DRSP

Alteration of PBPs

Amoxicillin/clavulanate for infections in infants and children: past, present and future : Pediatr Infect Dis J, 2003;22:S139-48

Adverse effect

- Skin rash : most common adverse effect and hypersensitivity responses
  - anaphylaxis
  - Stevens-Johnson syndrome
- Gastrointestinal
  - nausea, vomiting, diarrhea
  - most common in response to ampicillin

- Neurological
  - seizures, confusion, hallucinations, paresthesias
  - PGS and procaine penicillin G
- Pseudomembranous colitis
  - less common

More serious adverse effects occur only when

- extremely high doses of the drug
- patient has significant renal impairment

Jarisch-Herxheimer reaction

ATB : Penicillins, Tetracyclines, Erythromycin

extracellular spirochete in plasma

Syphilis, Leptospirosis, Lyme disease

spirochete breakdown in blood circulation

IL-6
IL-8
TNF-alpha

cytokines

toxins

Acute inflammatory reaction

- symptoms usually begin 2 hr after ATB
- self-limited resolved within 24 hr

- cycles of fever (38-41 C)
- flu-like symptoms : malaise, chills, headache
- tachycardia, hypotension, skin rash

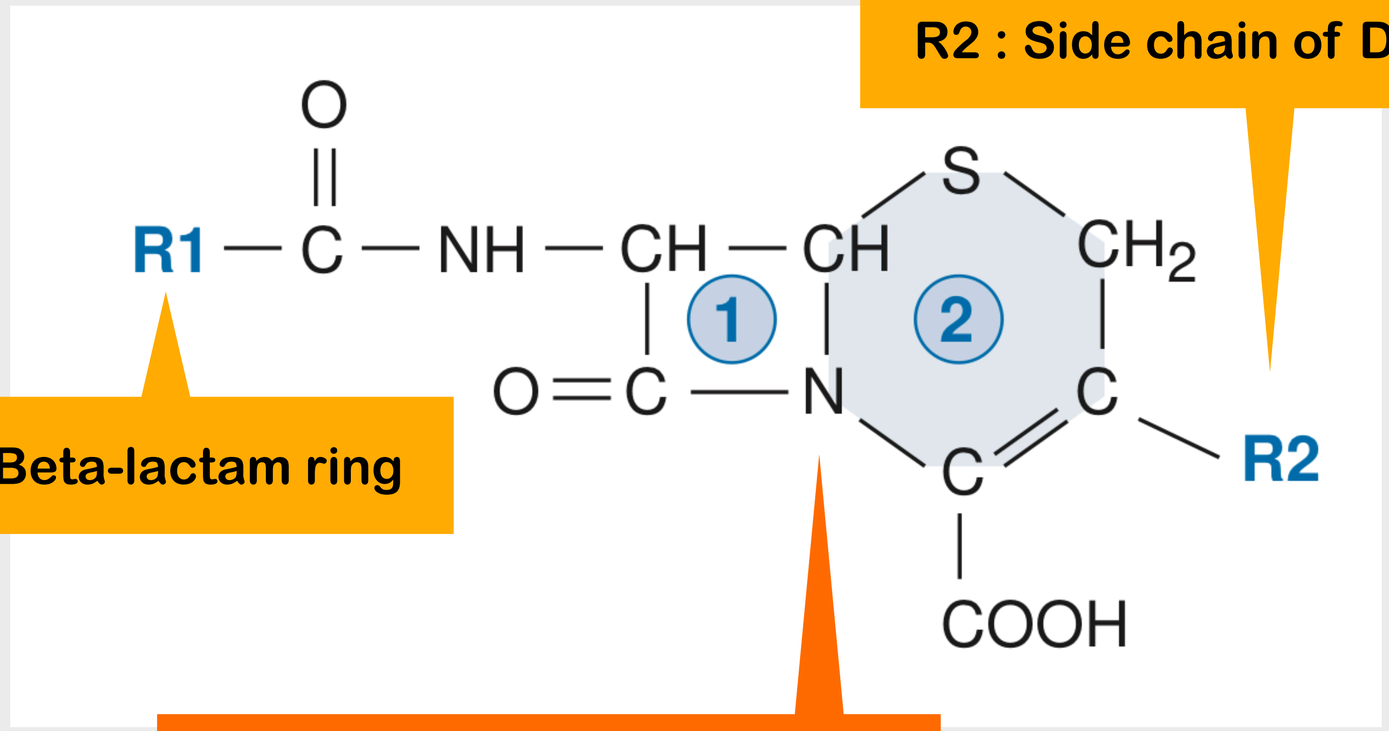
Jarisch Herxheimer Reaction. [Updated 2022 Apr 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

Cephalosporins

Cephalosporins

- from the fungus Cephalosporium acremonium

R2 : Side chain of Dihydrothiazine ring



R1 : Side chain of Beta-lactam ring

1. Beta-lactam ring
2. Dihydrothiazine ring

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Cephalosporins

	Intravenous form	Oral form
1st	Cefazolin	Cephalexin
2nd	Cefuroxime, Cefoxitine*, Cefotetan*	Cefuroxime, Cefaclor, Cefprozil
3th	Ceftriaxone, Cefotaxime, Ceftazidime	Cefdinir, Cefditoren, Cefixime
4th	Cefepime	-
5th	Ceftaroline	-

* Cephamycin

1st generation Cephalosporins

Cefazolin, Cephalexin

- Capable of protecting from cleavage by staphylococcal β-lactamases
- No activity against H. influenzae
- Do not achieve therapeutic CSF concentration

Gram-positive	S. aureus Streptococci
Gram-negative	P. mirabilis E. coli K. pneumoniae

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

2nd generation Cephalosporins

Cefuroxime
Cephamycins (cefoxitin, cefotetan)

- Broaden coverage against respiratory gram-negative pathogens
- Cephamycins
  - not actually cephalosporins
  - isolated from the bacterium Streptomyces lactamdurans
  - methoxy group in place of hydrogen on Beta-lactam ring

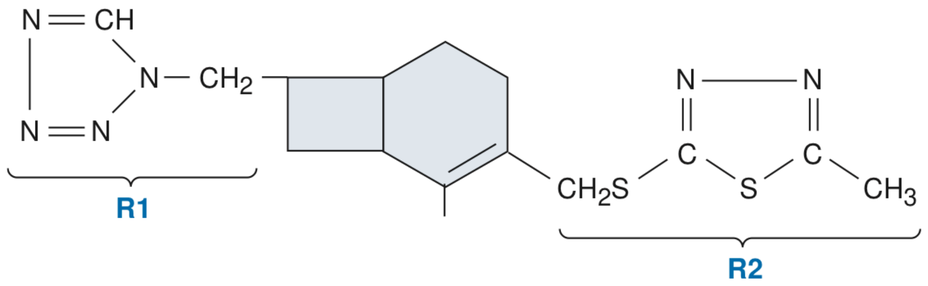


FIGURE 5-11. Structure of cefazolin.

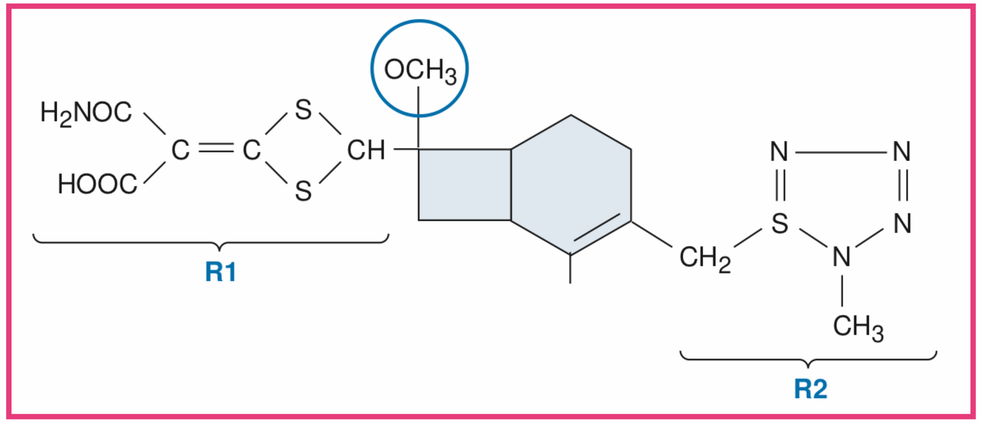


FIGURE 5-12. Structure of cefotetan. The methoxy group characteristic of the cephamycins is circled.

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008
Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

2nd generation Cephalosporins

Cefuroxime
Cephamycins (cefoxitin, cefotetan)

- Cover both gram positive and negative bacteria
  - less S. aureus activity than 1st generation
  - less gram-negative activity than 3rd generation
- Cefuroxime
  - respiratory infections (acute otitis media, pneumonia, acute bacterial sinusitis)
  - S. aureus skin & soft-tissue infection
  - E. coli UTI
- Cephamycin : intra-abdominal or intrapelvic infection/surgical prophylaxis

Gram-positive	S. aureus Streptococci
Gram-negative	H. influenzae E. coli N. meningitidis M. catarrhalis
Anaerobe	Bacteroides fragilis (cephamycins)

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

3rd generation Cephalosporins

	Ceftriaxone	Cefotaxime	Ceftazidime
Gram-positive	Streptococci (except PSNP* in CSF) Staphylococcus aureus		-
Gram-negative	Community-acquired : H. influenza, M. catarrhalis, many Enterobacteriaceae (E. coli, K. pneumoniae, Proteus, Enterobacter spp.)		
			Pseudomonas aeruginosa
Bilirubin displacement	displace	non-displace prefer in neonate	non-displace
Interval	12-24 hr	6-8 hr	8 hr

PNSP : penicillin-nonsusceptible Streptococcus pneumoniae

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

3rd generation Cephalosporins

Cefdinir (Omnicef), Cefditoren, Cefpodoxime (Banan)
Cefixime (Cefspan), Ceftibuten (Cedax)

- Skin & soft tissue infection
- Respiratory tract infection (drug-resistant S.pneumonia prefer Cefditoren)
  - acute otitis media
  - acute bacterial sinusitis
  - GAS pharyngitis (Penicillin allergy)
  - bacterial pneumonia
- Urinary tract infection (Cefixime, Ceftibuten)

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

4th generation Cephalosporins

Cefepime, Cepirome

- Modifications of the R2 side chain of the 3rd-generation cephalosporins
- Antipseudomonal activity without loss of antistaphylococcal activity

Gram-positive	Staphylococcus aureus Streptococci (except PSNP* in CSF)
Gram-negative	same as ceftazidime Pseudomonas aeruginosa Enterobacteriaceae AmpC

PNSP : penicillin-nonsusceptible Streptococcus pneumoniae

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

5th generation Cephalosporins

Ceftaroline

- Expanded activity against gram-positive cocci
- Similar to Ceftriaxone
  - against gram-negative bacteria
  - lack of antipseudomonal activity

Gram-positive	MRSA, MRSE DRSP
Gram-negative	same as ceftriaxone

MRSA : Methicillin-resistant S. aureus
MRSE : Methicillin-resistant S. epidermidis
DRSP : drug-resistant S. pneumoniae

Ceftaroline: A New Cephalosporin with Activity against Methicillin-Resistant Staphylococcus aureus (MRSA), Clin Med Rev Ther, 2011
Basics for Clinicians: The ABCs of Choosing the Right Antibacterial Agent (2nd edition), 2013

Beta-lactam plus Beta-lactamase inhibitors

Cefoperazone-sulbactam

Gram-positive	Staphylococcus Streptococci
Gram-negative	Enterobacteriaceae ESBL, AmpC Carbapenem-resistant Acinetobacter baumannii
Anaerobe	Bacteroides spp.

Cefoperazone/sulbactam: New composites against multiresistant gram negative bacteria : Infect Genet Evol. 2021, Mar;88:104707

Adverse effect

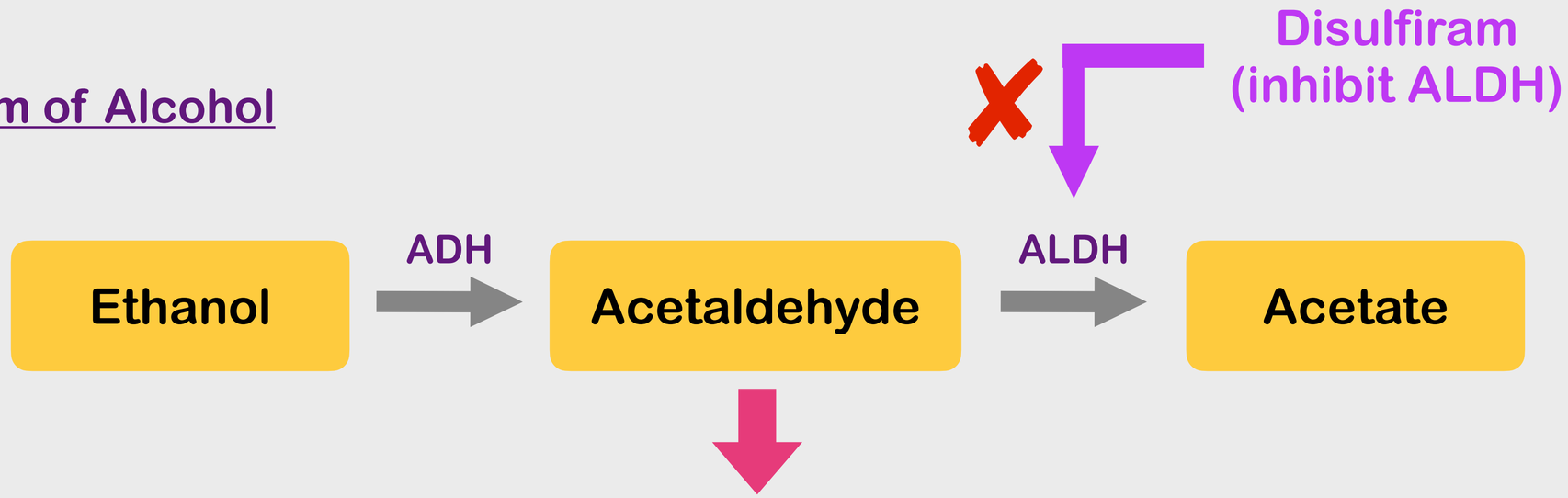
- Common
  - Gastrointestinal : common
    - nausea, vomiting, diarrhea
    - occur with orally administered
  - Drug fever

- Rare
  - Pseudomembranous colitis
  - Mild nephrotoxicity and hepatic enzyme elevation
  - Thrombocytopenia, leukopenia, eosinophilia

Cephalosporins:A Review, Pediatrics in Review, Vol.29 No.8 August 2008

Disulfiram-like reaction

Metabolism of Alcohol



high serum Acetaldehyde

- mild reaction : facial flushing, nausea, vomiting, headache
- severe reaction : angioedema, hypotension, shock, death

Cephalosporin affect metabolism of alcohol

ADH : alcohol dehydrogenase, ALDH : aldehyde dehydrogenase

Disulfiram-like Reaction Involving Ceftriaxone in a Pediatric Patient. J Pediatr Pharmacol Ther. 2018;23(2):168-171.

Serum sickness-like reaction

- Cefaclor in young children
- Clinically resembles true serum sickness but less severe, onset 1-3 wk
  - fever : low-grade
  - rash : urticaria
  - arthralgia : MCP, wrists, ankles, knees, shoulder
- Metabolites --> act similarly to haptens that bind plasma proteins --> induce abnormal immunologic response
- Not associated with antigen-antibody complex formation and normal complement level
- Treatment : glucocorticoid, antihistamine (no evidence of efficacy)

SUMMARY

Penicillin

- Natural penicillin : spirochete, GAS infection
- Cloxacillin : MSSA
- Ampicillin : L. monocytogenes, Enterococci
- Piperacillin : Pseudomonas
- BL+BI
  - Augmentin oral : S. aureus (4:1, 7:1), S. pneumoniae (14:1)
  - cover ESBL, anaerobe
  - Tazocin : Pseudomonas

SUMMARY

Cephalosporin

- Increase gram-negative activity in each higher generation
- Decreases gram-positive activity with increasing generation except for the 1st and 4th-generation drugs
- Cefoxitin : Cephamycin not true cephalosporin, most anaerobic activity
- Ceftriaxone : the least frequent dosing, bilirubin displacement
- Cefepime and Ceftazidime : anti-Pseudomonas
- Cefepime : AmpC beta-lactamase
- Enterococci, ESBL : resistant to all cephalosporins

THANK YOU