General Microbiology Course

(Antibiotics A & B)

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Objectives

- **Some history highlights**
- **Structure of Gram positive and negative bacteria cell wall**
- **Targets of the antibacterial drugs**
- **Mechanisms of action of antibacterial drugs**
- **The mechanisms of antibacterial resistance**

Discovery of Antimicrobial Agents

Antibacterial agents which inhibit bacterial cell wall synthesis was discovered by Fleming from a fungal colony (1928)

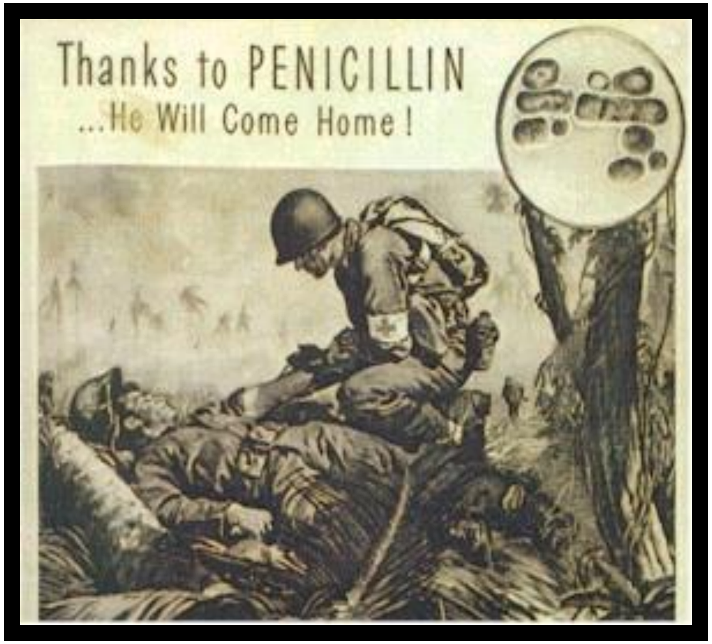
Sir Alexander Fleming

The product of the mold was named penicillin, after the Penicillium mold from which it was derived

Isolated and purified by Florey and Chain (1938)

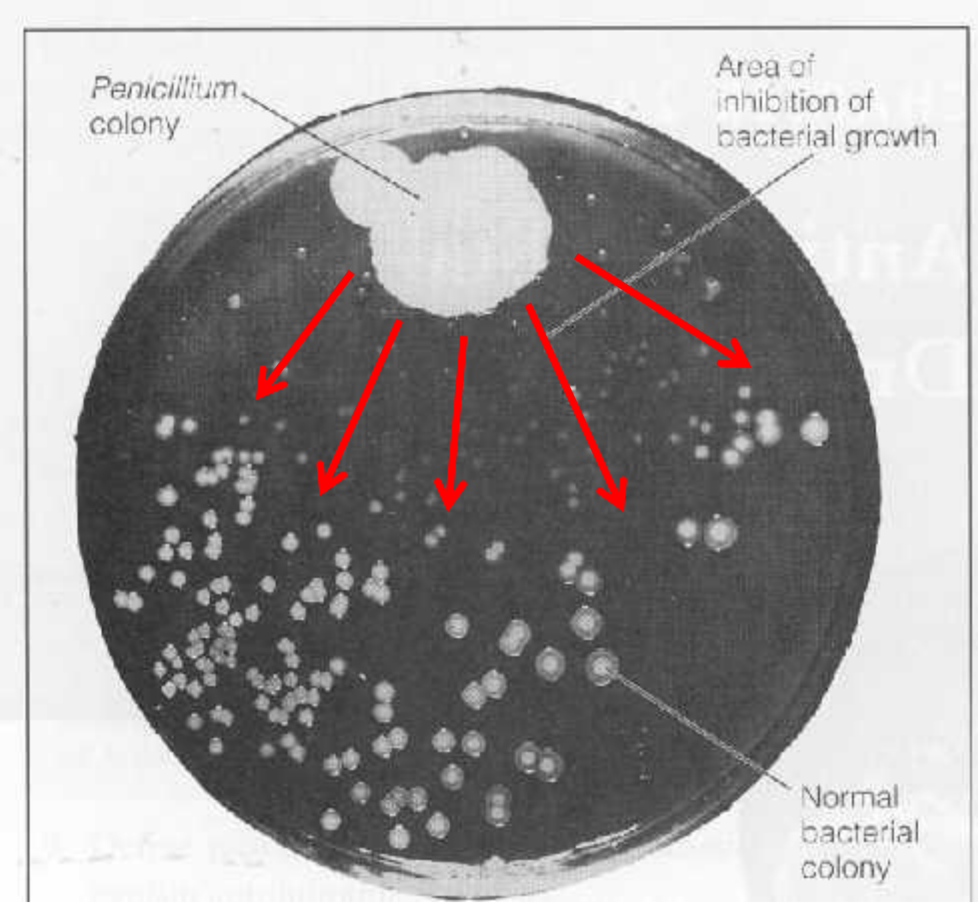
First successful clinical trial (1941)

Development of semi-synthetic penicillins (1958-1960)



Discovery of Antimicrobial Agents

Fleming's Petri Dish

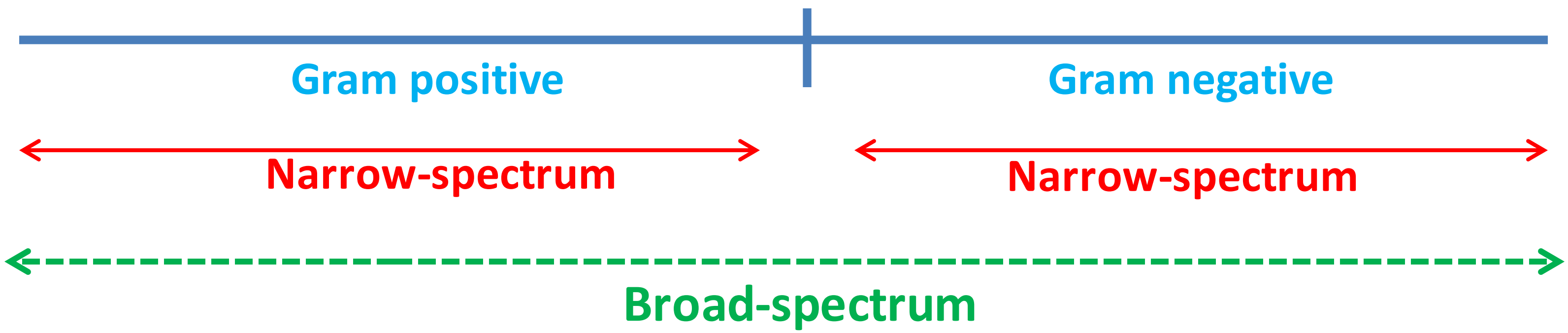


antibiosis = against life

Definitions

Antibiotics are classified based on

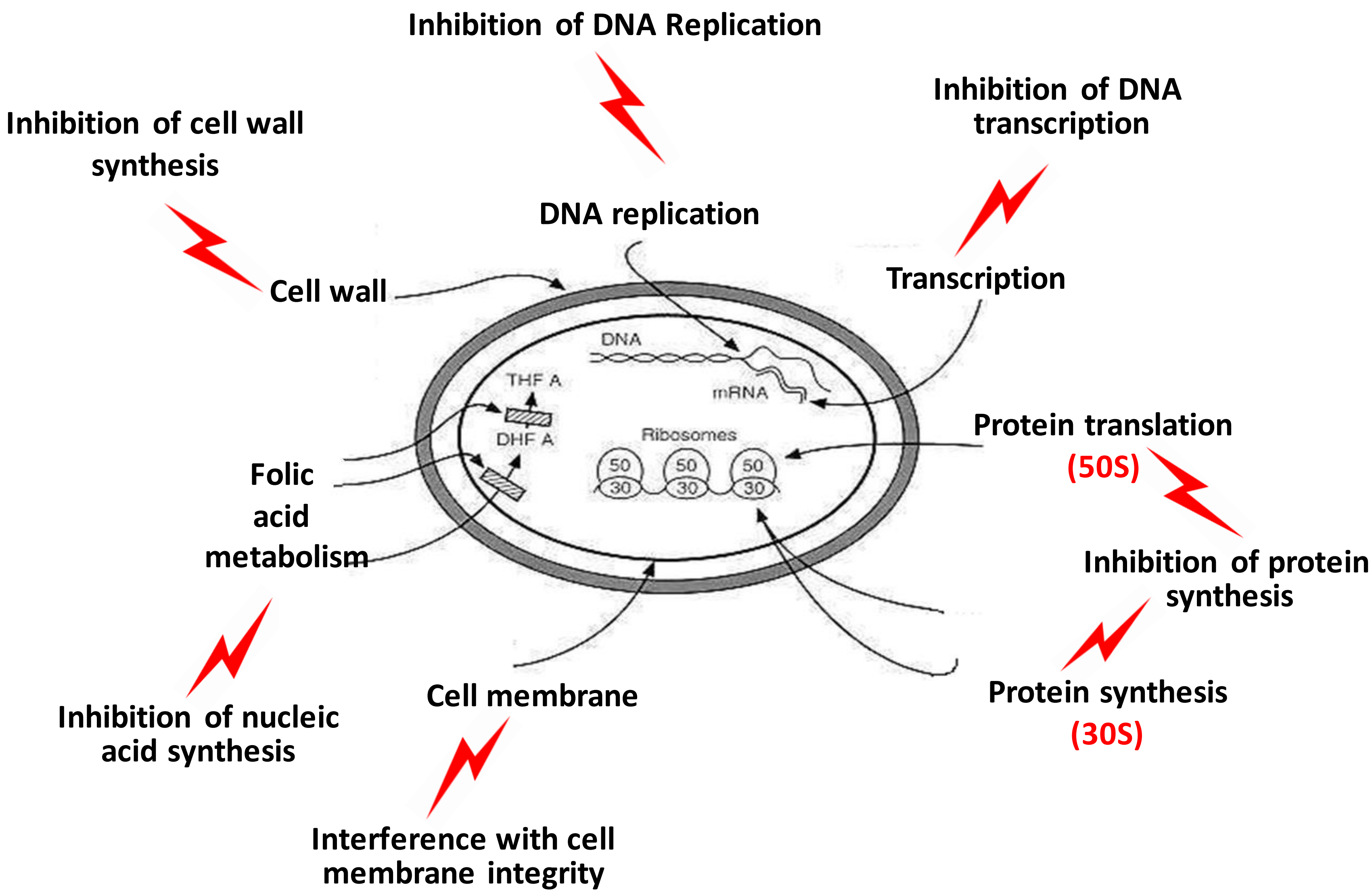
1. **Target-specificity or antimicrobial spectrum:** the range that a drug kills or suppresses the growth of microorganisms.
   - ✓ **Narrow-spectrum: the drugs that only act** on Gram positive or Gram negative bacteria.
   - ✓ **Broad-spectrum: the drugs that have act** on Gram positive & Gram negative bacteria.



2. Killing bacteria or prevent cell division

- ✓ **Bactericidal:** antibiotic that kills bacteria
- ✓ **Bacteriostatic**: antibiotic that prevents bacterial cell division

Mechanisms of Action of Antibacterial Drugs



Mechanisms of Action of Antibacterial Drugs

Inhibition of cell wall synthesis

- **Cycloserine**
- **Polypeptides**
  - Bacitracin
  - Actinomycin
  - Colistin
  - Polymyxin B
- **Glycopeptides**
  - Vancomycin
  - Tecoplanin
- **Beta-lactam antibiotics**
  - Penicillins
  - Cephalosporines
  - Carbapenems
  - Monobactams

Cephalosporin Antibiotics
Made Easy - Simple Trick!!

1st Generation
"FA/PHA"

* CEFAZOLIN
CEFADROXIL
* CEPHALEXIN
CEPHALOTHIN
CEPHAPIRIN
CEPHRADINE

2nd gen
"Furry fox face tanned by a pro"

Cefuroxime
Cefoxitin
Cefaclor
Cefotetan
Cefprozil

Cefaclor and Cefuroxime are 2nd generation

3rd Generation
"ONE/TEN/IME"

* CEFTRIAXONE
CEFTIBUTEN
* CEFOTAXIME
* CEFTAZIDIME
CEFPODOXIME
CEFIXIME

4th Generation
"PI"

* CEFEPIME
CEFPIROME

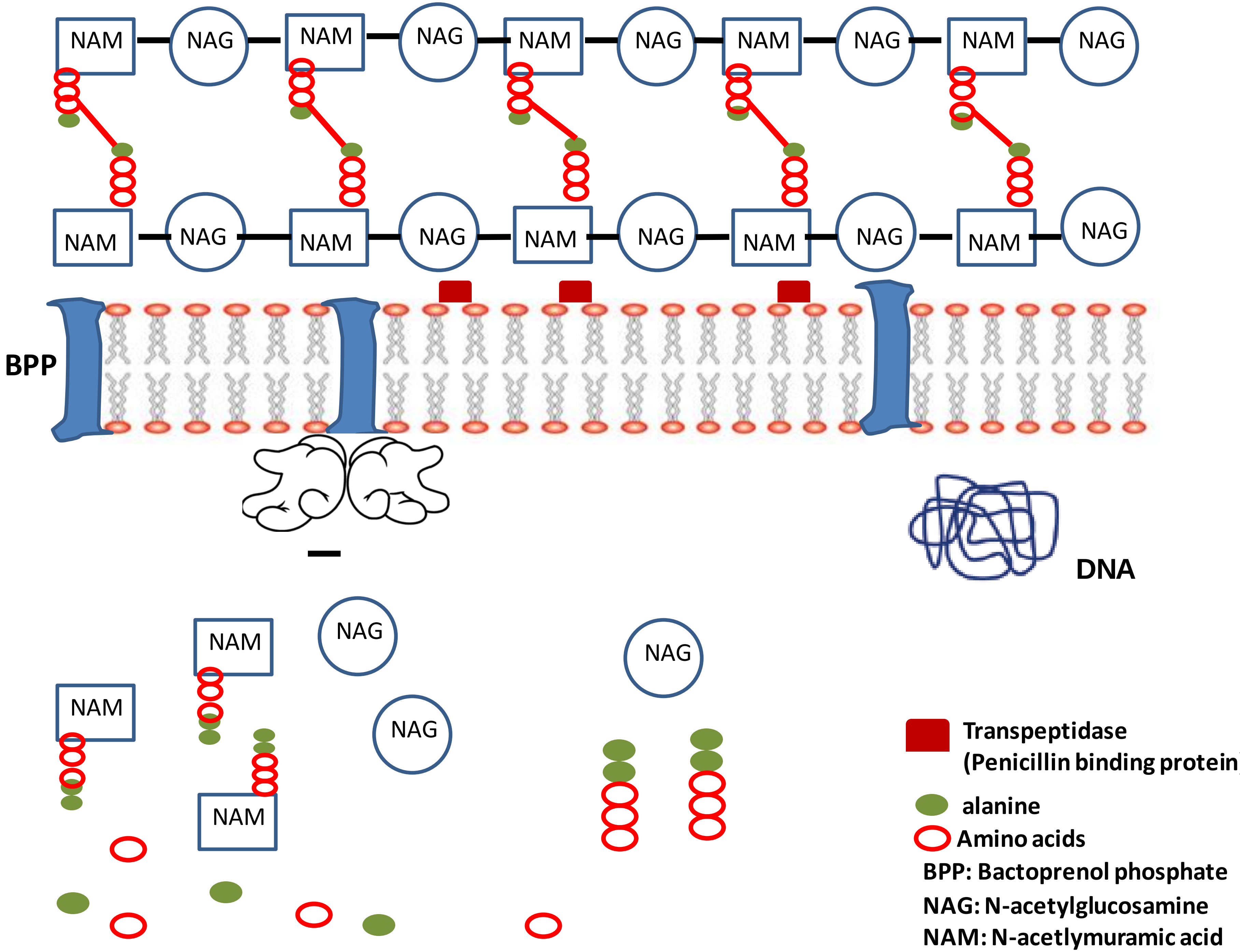
5th gen
"ceft-l"

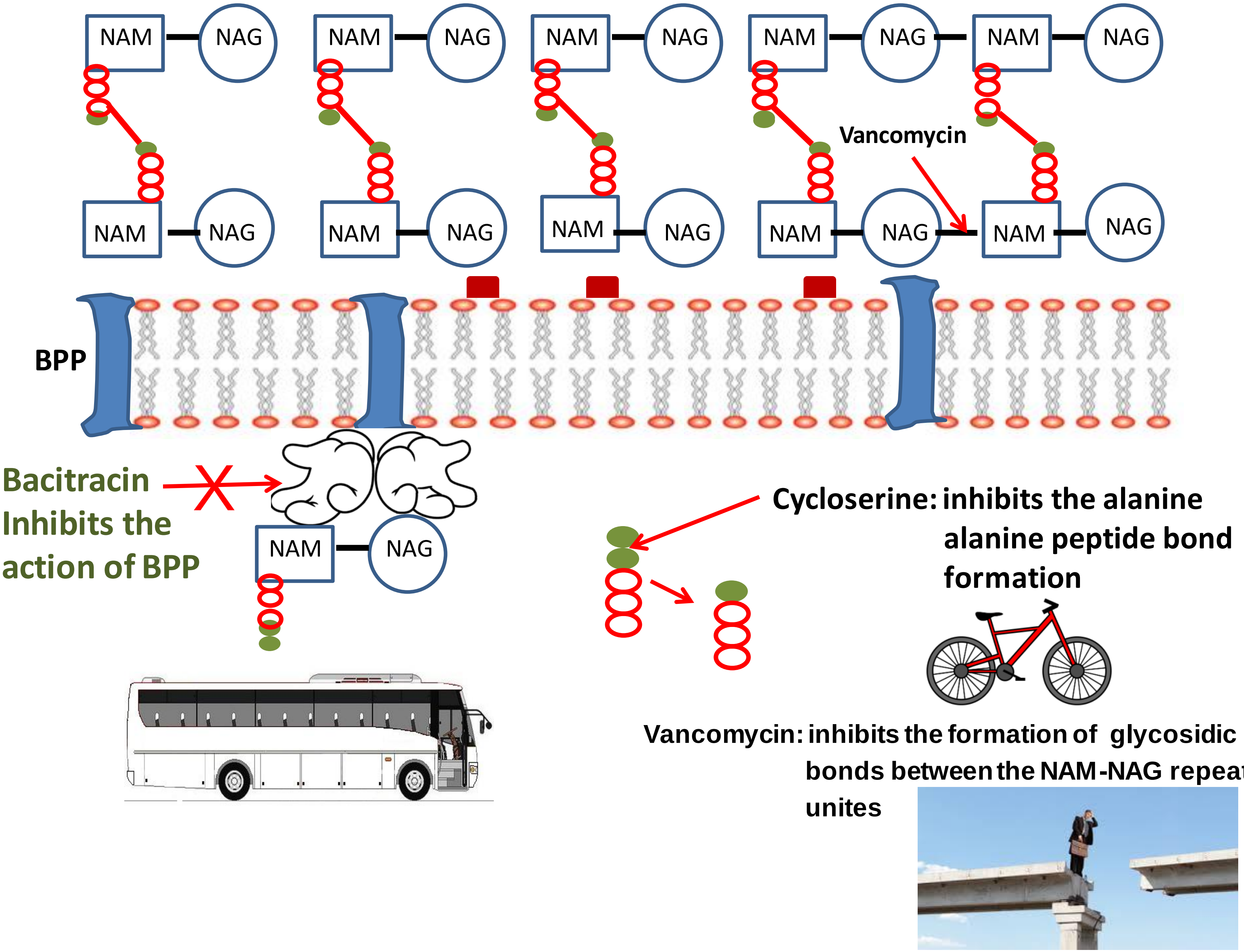
Ceftobiprole
Ceftolozane
Ceftaroline

Gram coverage

	1st Gen	2nd Gen	3rd Gen	4th Gen	5th Gen
				Pseudomonas	MRSA
Gram +	+++	++	+	++	++
Gram -	-	- -	- - -	- - -	- - -

Gram + → Gram - → Pseudomonas → MRSA

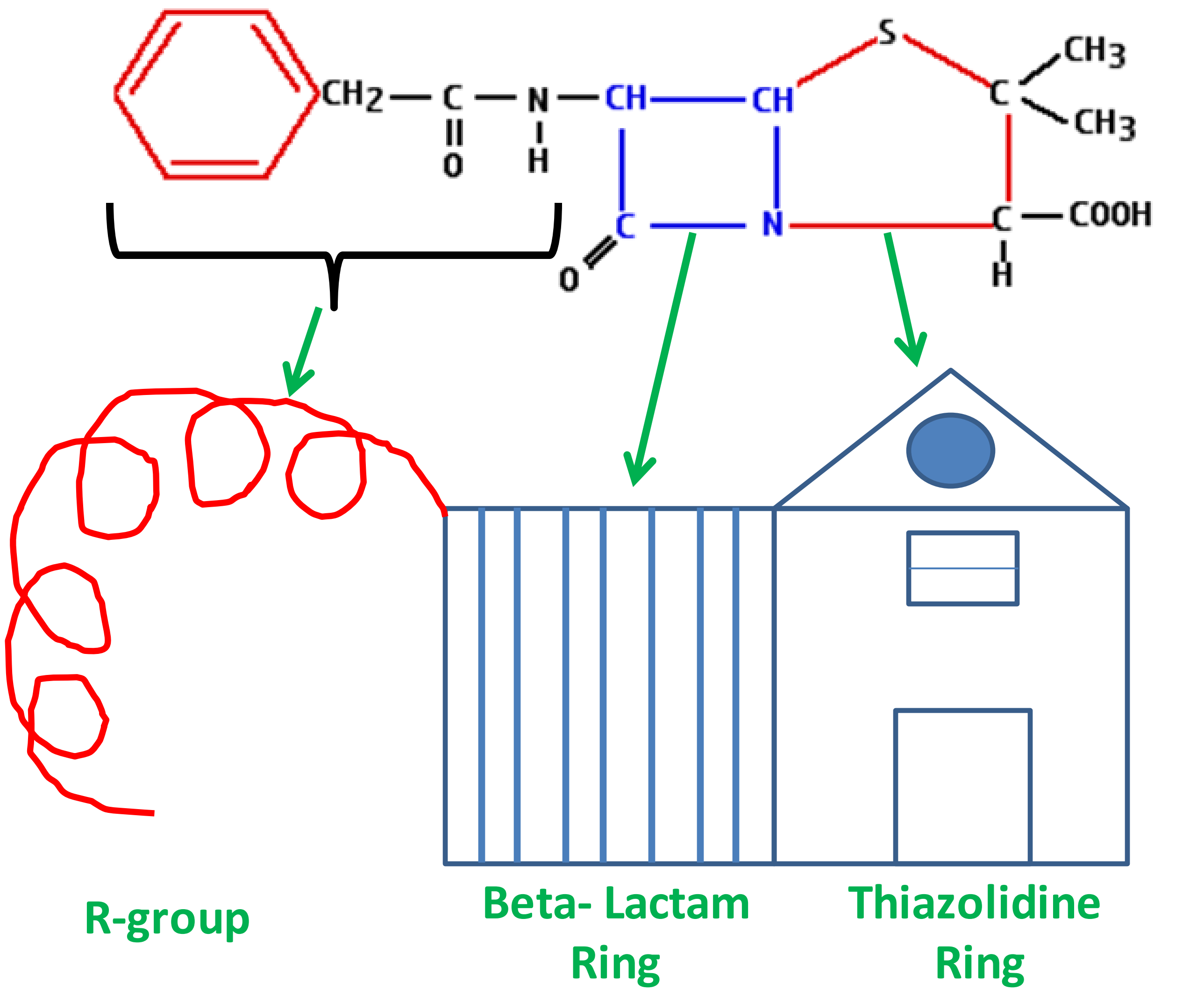

NAM
NAG
BPP
DNA
Transpeptidase
(Penicillin binding protein)
alanine
Amino acids
BPP: Bactoprenol phosphate
NAG: N-acetylglucosamine
NAM: N-acetlymuramic acid


NAM
NAG
Vancomycin
BPP
Bacitracin
Inhibits the
action of BPP
Cycloserine: inhibits the alanine
alanine peptide bond
formation
Vancomycin: inhibits the formation of glycosidic
bonds between the NAM-NAG repeat
unites

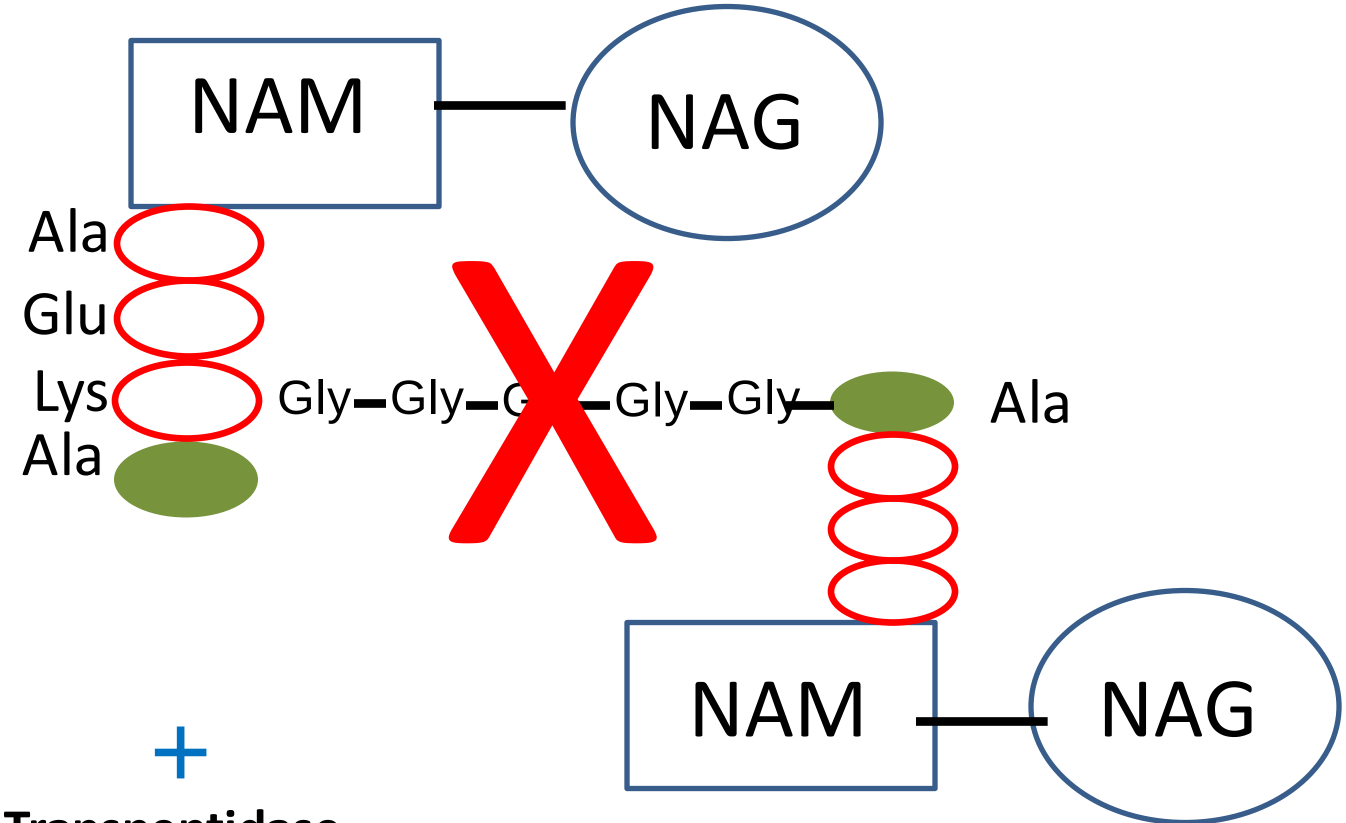
Mechanisms of Action of Antibacterial Drugs

Inhibition of cell wall synthesis

Structure of penicillin



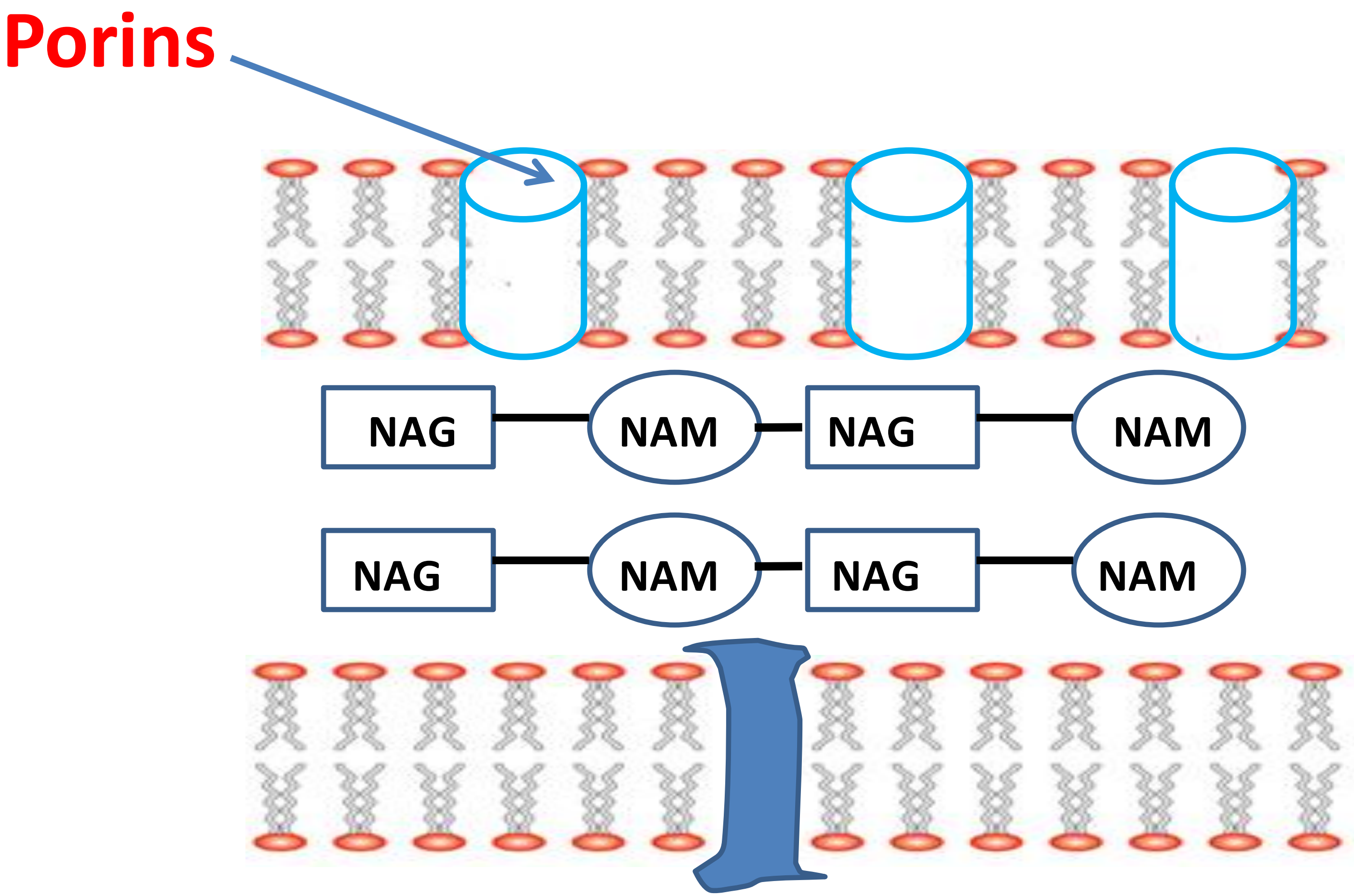
Mechanism of action - bacterial cell wall synthesis



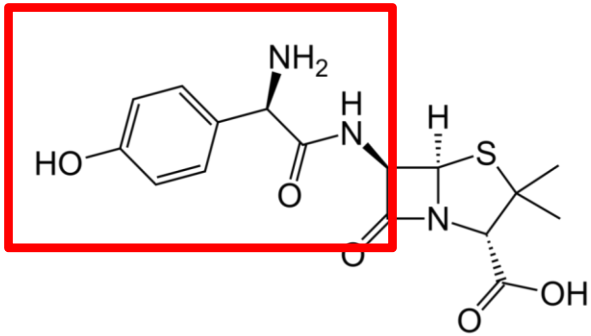
Transpeptidase
(Penicillin binding protein)

Penicillin inhibits the action of this enzyme

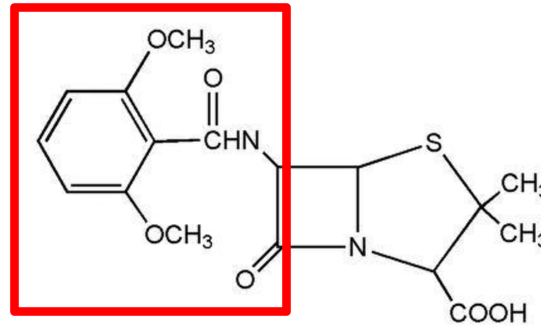
Gram negative bacterial cell wall structure



Mechanisms of Action of Antibacterial Drugs

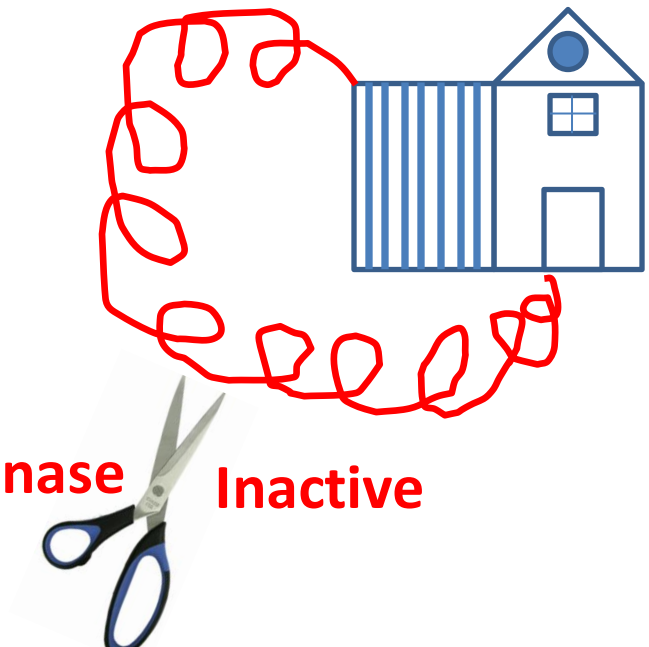


Amoxicillin



Methicillin

Penicillinase



Penicillinase

Inactive

Mechanisms of Action of Antibacterial Drugs

Inhibition of cell wall synthesis

Penicillins

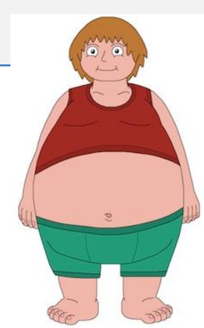
- Narrow spectrum
  - Narrow spectrum
    - Penicillin G
    - Penicillin V
  - Very very narrow spectrum
    - Methicillin
    - Nafcillin
    - Cloxacillin
    - Dicloxacillin
    - Flucloxacillin
- Wide spectrum
  - Smart wide spectrum
    - Amoxicillin
    - Ampicillin
  - Very Smart wide spectrum
    - Mezlocillin
    - Piperacillin
    - Ticarcillin
    - Carbenicillin

Q: Why do penicillins vary in their range against Gram-positive and negative bacteria?

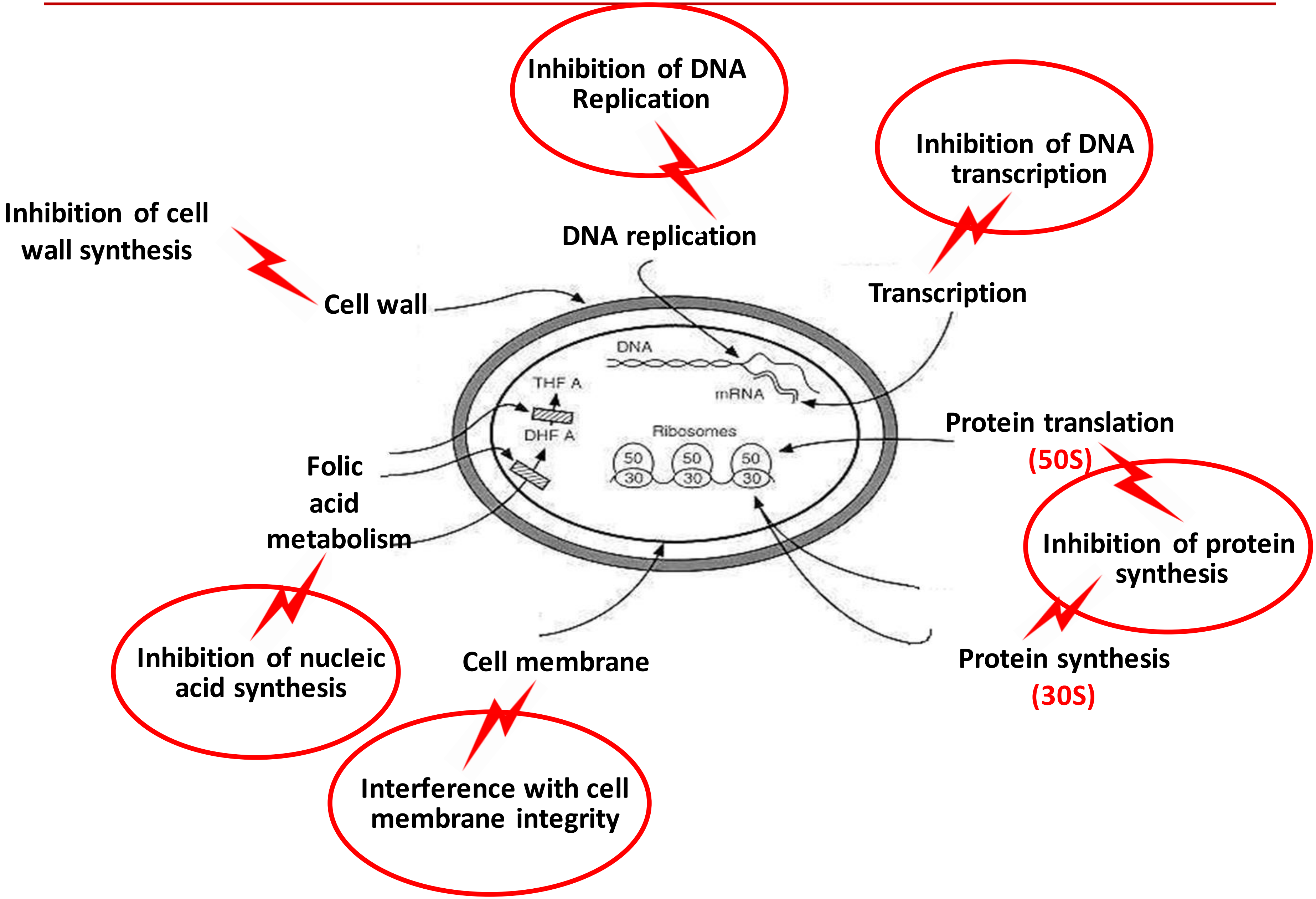
This depends on the penicillin molecular size which is determined by the R- group

Penicillins

- Narrow spectrum
  - **Narrow spectrum**: bulky (moderately large R group): they go only through Gram positive bacteria
  - **Very very narrow spectrum**: Developed to overcome the staphylococcal resistant to the natural penicillin due the production of penicillinase. They are very bulky and they can only penetrate the peptidoglycan *Staphylococci* and therefore they are called anti- staphylococcal antibiotics
- Wide spectrum
  - **Smart wide spectrum**: Against all bacteria except *Pseudomonas*
  - **Very Smart wide spectrum**: Developed against Pseudomonas Because *Pseudomonas* porins are vey narrow



Mechanisms of Action of Antibacterial Drugs



Inhibition of protein synthesis

Antimicrobials that Bind to the 30S Ribosomal Subunit

Aminoglycosides

Streptomycin
Kanamycin
Gentamicin
Tobramycin
Amikacin
Netilmicin
Spectinomycin
neomycin (topical)

Tetracyclines

Minocycline
doxycycline

Inhibition of protein synthesis

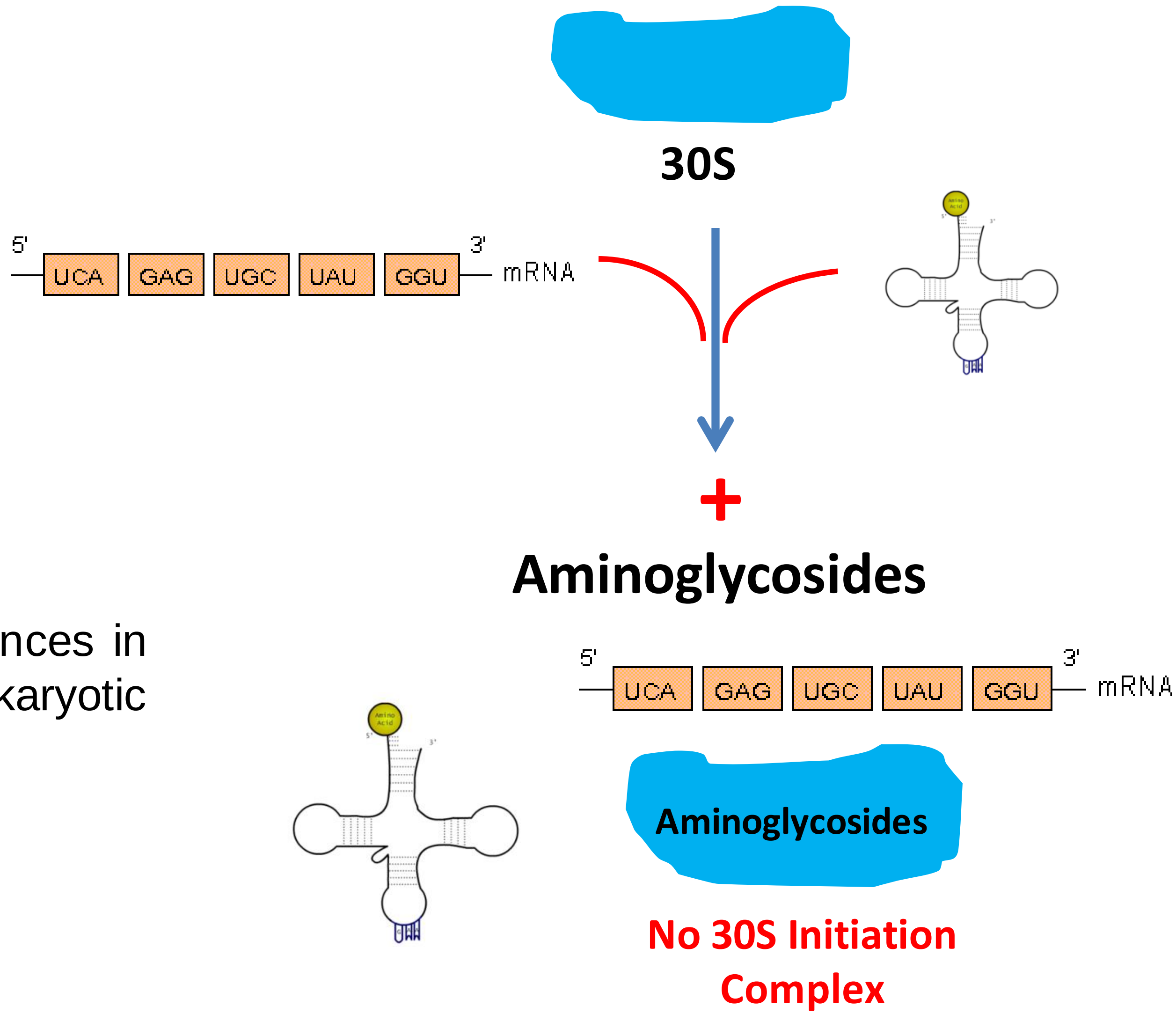
Antimicrobials that Bind to the 30S Ribosomal Subunit

Aminoglycosides

- They irreversibly bind to the 30S and eventually they will freeze the initiation complex (30S-mRNA-tRNA) so that no further initiation can occur.

-Selectivity due to differences in prokaryotic and eukaryotic ribosomes

-**Resistance** – Common



Inhibition of protein synthesis

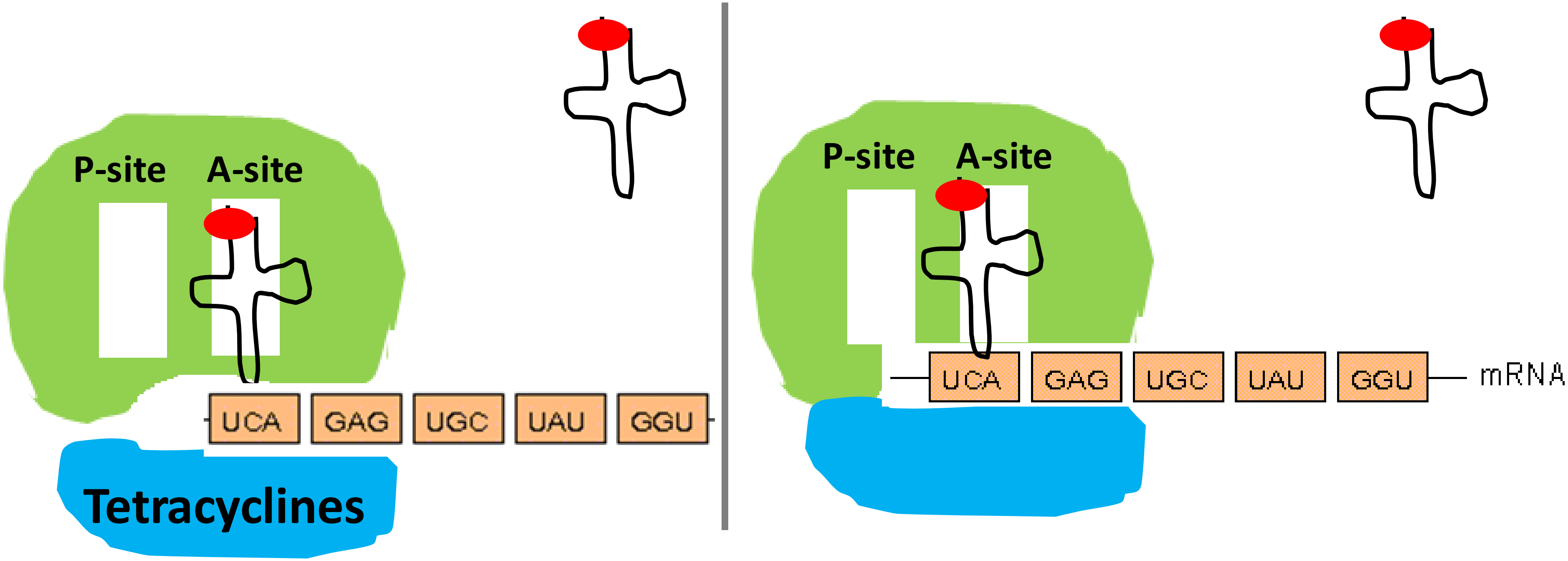
Antimicrobials that Bind to the 30S Ribosomal Subunit

Tetracyclines

Mode of action - The tetracyclines reversibly bind to the 30S ribosome and inhibit binding of aminoacyl-t-RNA to the acceptor site on the 70S ribosome.

Spectrum of activity - Broad spectrum; Useful against intracellular bacteria

Resistance – Common



70S Initiation Complex

Antimicrobials that Bind to the 50S Ribosomal Subunit

Inhibition of protein synthesis

Antimicrobials that Bind to the 50S Ribosomal Subunit

- **Amphenicols**
  - Chloramphenicol
- **Lincosamides**
  - Lincomycin
  - Clindamycin
- **Macrolides**
  - Erythromycin
  - Clarithromycin
  - Azithromycin

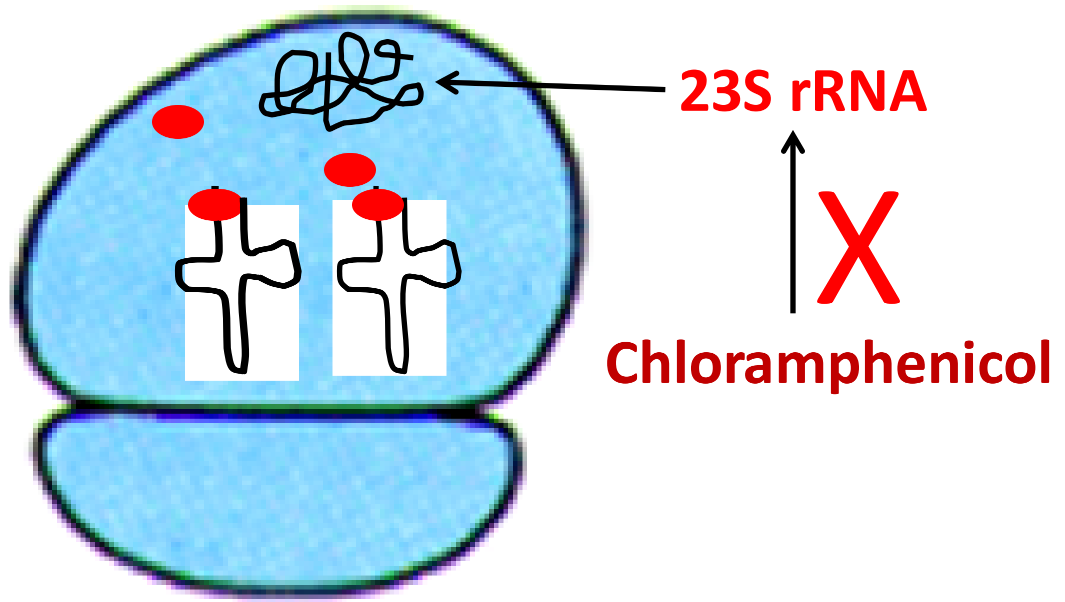
Inhibition of protein synthesis

Antimicrobials that Bind to the 50S Ribosomal Subunit

Amphenicols and Lincosamides

Mode of action - These antimicrobials bind to the 50S ribosome and inhibit peptidyl transferase activity of the 23S rRNA.

- **Resistance** - Common

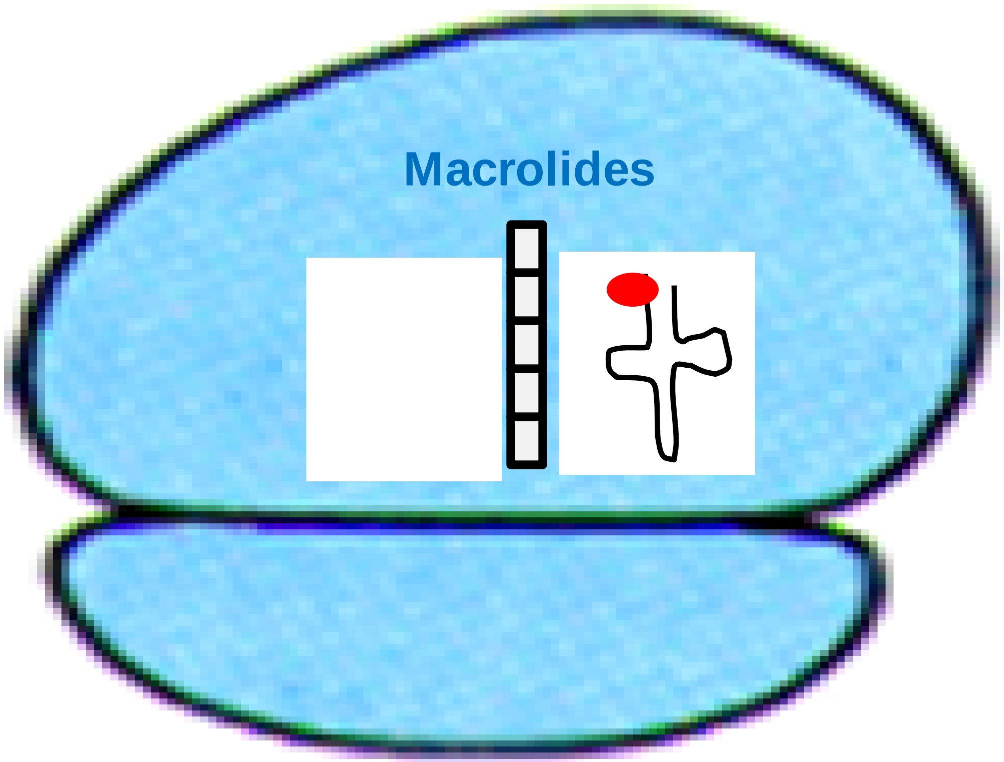


Inhibition of protein synthesis

Antimicrobials that Bind to the 50S Ribosomal Subunit

Macrolides :erythromycin, clarithromycin, azithromycin

- **Mode of action** - The macrolides inhibit translocation.
  - **Spectrum of activity**: Gram-positive bacteria, *Mycoplasma, Legionella*
  - **Resistance:** common



Inhibitors of RNA Synthesis

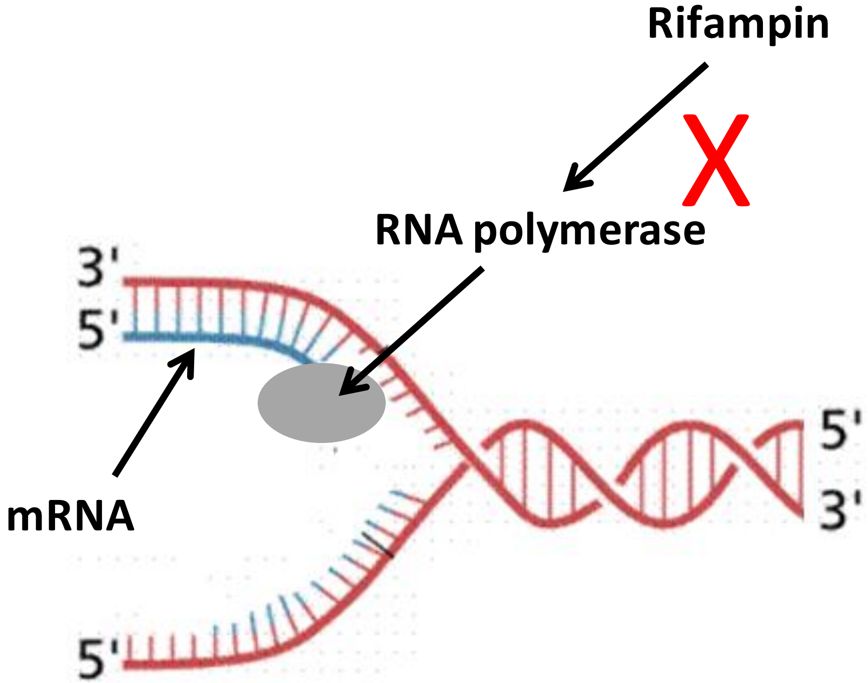
Rifamycins group:

Rifampin, Rifampicin, Rifabutin

Selectivity due to differences between prokaryotic and eukaryotic RNA polymerase

Mode of action: these antimicrobials bind to DNA-dependent RNA polymerase and inhibit initiation of mRNA synthesis.

Resistance: Common



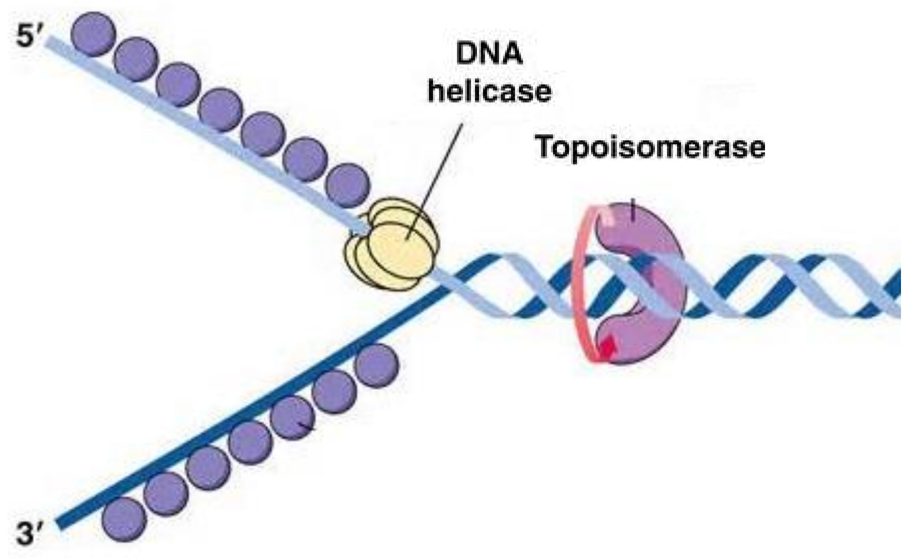
Inhibitors of DNA Synthesis

Fluoroquinolones:

nalidixic acid, ciprofloxacin, ofloxacin, norfloxacin, levofloxacin.

Mode of action - These antimicrobials bind to the A subunit of DNA gyrase (topoisomerase) and prevent supercoiling of DNA, thereby inhibiting DNA synthesis.

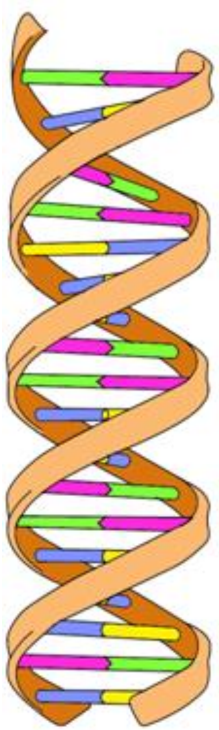
Resistance - Common for nalidixic acid



Inhibition of nucleic acid synthesis

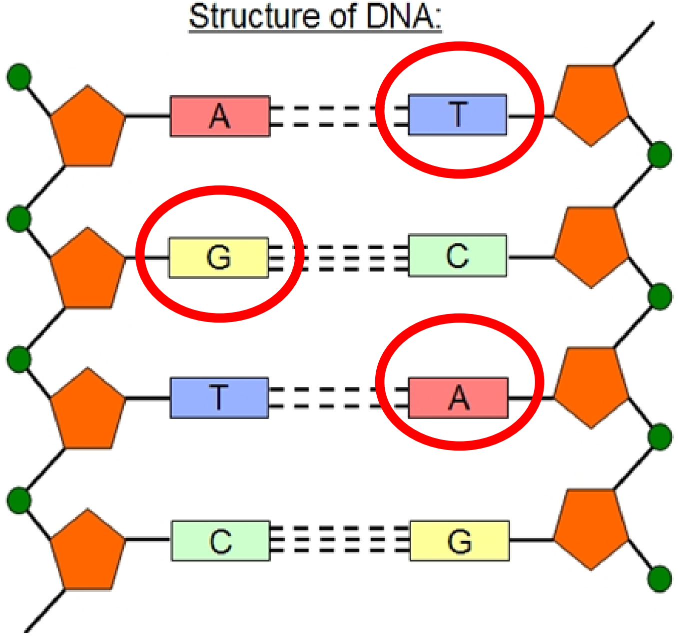
Nucleic acid synthesis is inhibited by:

1. **Trimethoprim**
2. **Sulfonamide group:** Sulfamethoxazole, Sulfadiazine Sulfathiazole, Sulfamerazine

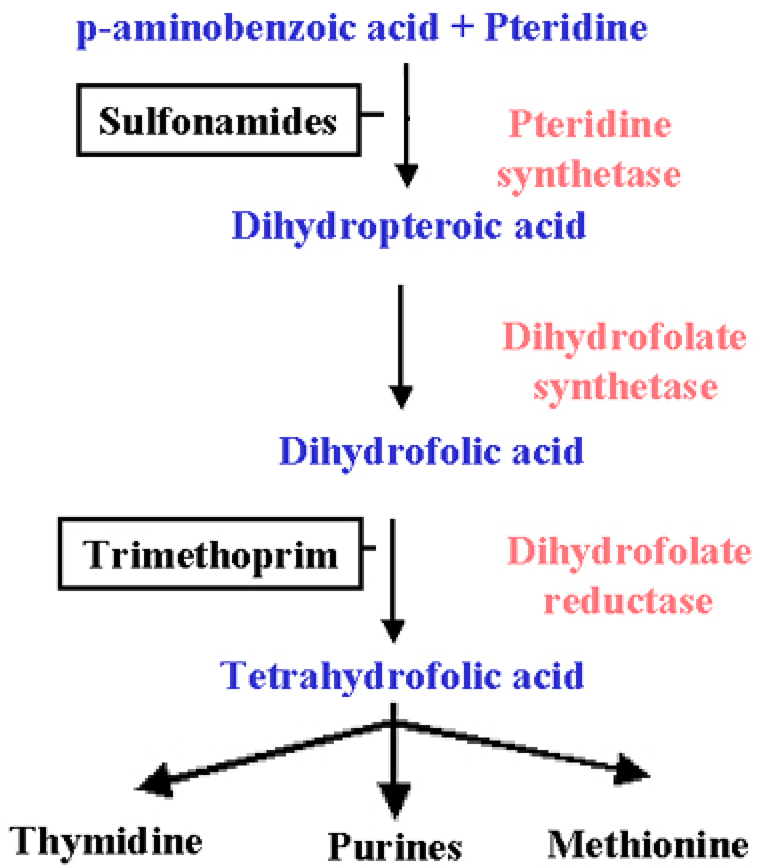


DNA

Structure of DNA:



Purine: adenine & guanine
Pyrimidine: cytosine & thymine



(Amino Acid)

Interference with cell membrane integrity

- Polymyxin B: binds to membrane of Gram negative bacteria and alters permeability
- This leads to leakage of cellular contents and cell death
- These drugs also bind to eukaryotic cells to some extent, which limits their use to topical applications

Antimicrobial Drug Resistance Principles and Definitions

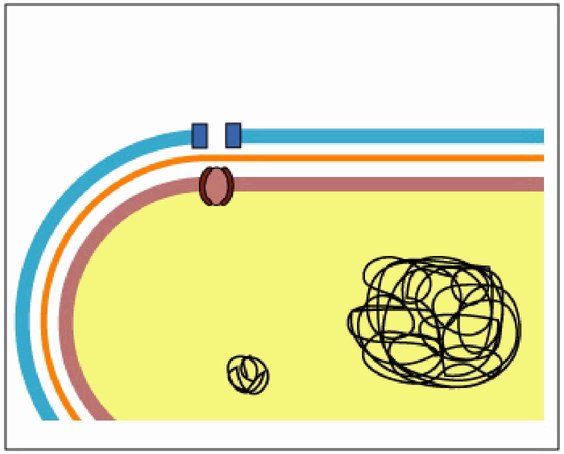
- Resistance can arise by mutation or by gene transfer (*e.g.* acquisition of a plasmid)

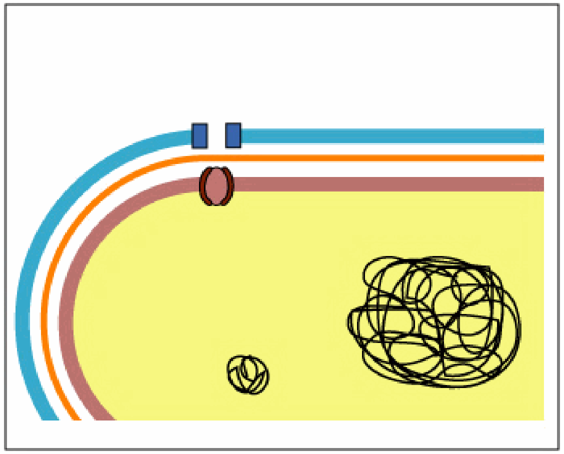
- Resistance provides a selective advantage

- Resistance can result from single or multiple steps

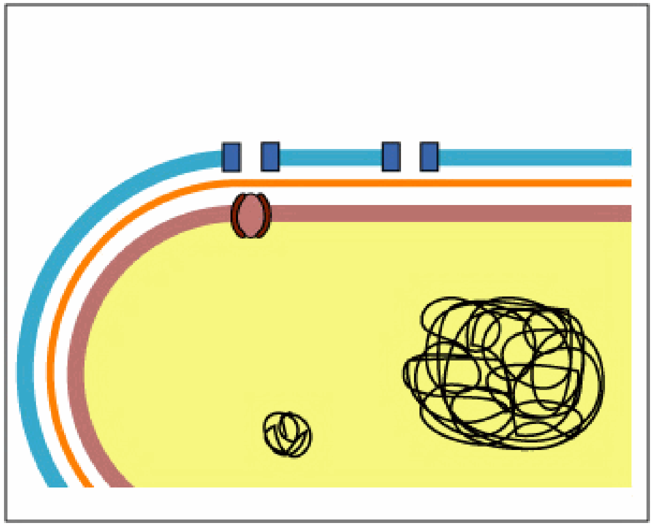
Principles of Antimicrobial Drug Resistance

- Altered permeability
  - Altered influx
    - Gram negative bacteria

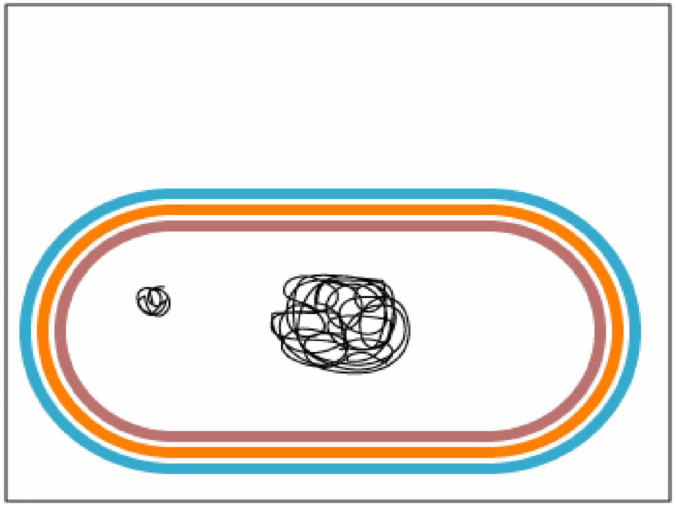




- Altered permeability
  - Altered efflux
    - tetracycline

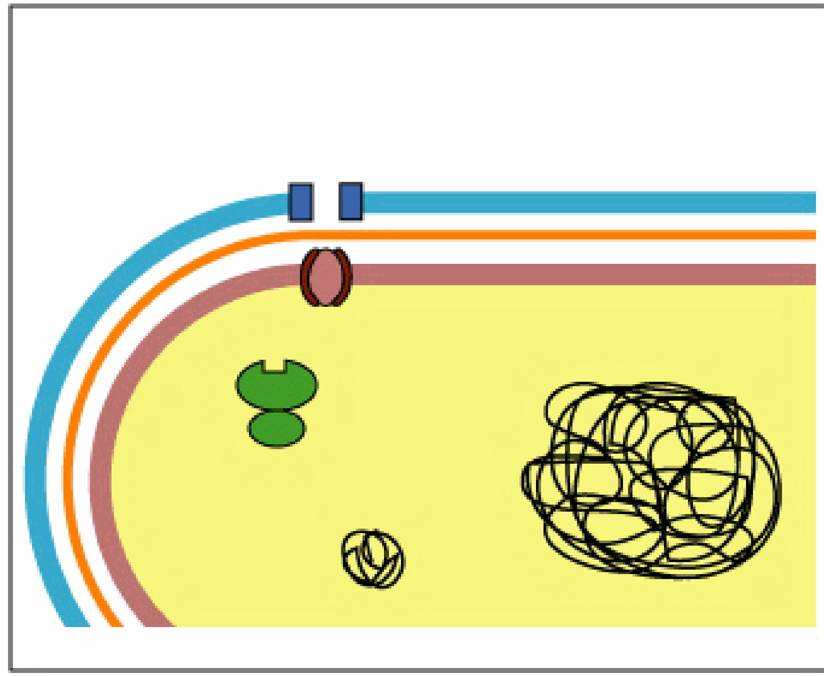


- Inactivation
  - ➢ Beta-lactamase



Antimicrobial Drug Resistance Principles and Definitions

- Altered target site
  - Penicillin binding proteins
  - RNA polymerase
  - 30S ribosome



Normal **Altered**


"How to Remember"

Antibiotic Classes

- **Mnemonic** to remember main antibiotic classes
- Tricks to remember the **names of antibiotics in each class**
- Trick to remember **gram coverage** of each antibiotic class.
- Trick to remember **mechanism of action** of each antibiotic class.

Antibiotics classes

Mnemonic

Antibiotic **C**an **T**erminate **P**rotein **S**ynthesis **F**or **M**icrobial **C**ells **L**ike **G**erms

1. Aminoglycosides
2. Cephalosporins
3. Tetracyclines
4. Penicillins
5. Sulfonamides
6. Fluoroquinolones
7. Macrolides
8. Carbapenems
9. Lincosamides
10. Glycopeptides

Antibiotic Classes

Mnemonic	Groups	Medication Names	Gram Coverage	Mechanism of Action
Antibiotics	Aminoglycosides	Streptomycin Gentamicin	Gram (-)	Inhibit Protein Synthesis (30s)
Can	Cephalosporins	Ceftriaxone Cefepime	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Terminate	Tetracyclines	Tetracycline Doxycycline	Gram (+)/(-)	Inhibit Protein Synthesis (30s)
Protein	Penicillins	Ampicillin Amoxicillin	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Synthesis	Sulfonamides	Sulfasalazine Sulfamethoxazole	Gram (+)/(-)	Inhibit Folate Synthesis
For	Fluoroquinolones	Ciprofloxacin Levofloxacin	Gram (+)/(-)	Inhibit DNA Replication
Microbial	Macrolides	Azithromycin Erythromycin	Gram (+)	Inhibit Protein Synthesis (50s)
Cells	Carbapenems	Meropenem Ertapenem	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Like	Lincosamides	Clindamycin	Gram (+)	Inhibit Protein Synthesis (50s)
Germs	Glycopeptides	Vancomycin	Gram (+)	Inhibit Cell Wall Synthesis

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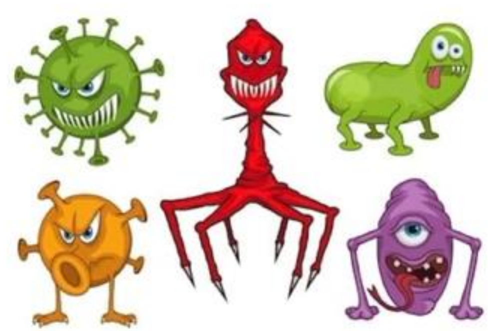
Antibiotics classes
Medication Names

1. Aminoglycosides	1. Mycin
2. Cephalosporins	2. Cef/Ceph
3. Tetracyclines	3. Cylines
4. Penicillins	4. Cillins
5. Sulfonamides	5. Sulfa
6. Fluoroquinolones	6. Floxacin
7. Macrolides	7. Thromycin
8. Carbapenems	8. Penem
9. Lincosamides	9. Mycin
10. Glycopeptides	10. In (Mycin)



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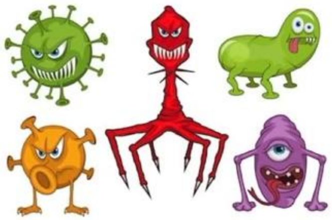
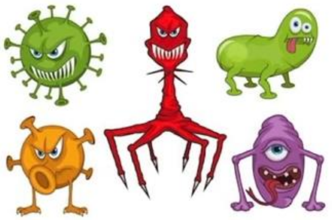


Antibiotics classes
Gram Coverage



1. AmiNoglycosides	1. Gram (-)=NO
2. Cephalosporins	2. Gram (+)(-)
3. Tetracyclines	3. Gram (+)(-)
4. Penicillins	4. Gram (+)(-)
5. Sulfonamides	5. Gram (+)(-)
6. Fluoroquinolones	6. Gram (+)(-)
7. Macrolides	7. Gram (+)
8. Carbapenems	8. Gram (+)(-)
9. Lincosamides	9. Gram (+)
10. Glycopeptides	10. Gram (+)

G L A M

Glycopeptides
Lincosamides
AmiNoglycosides
Macrolides

Antibiotic Classes

Mnemonic	Groups	Medication Names	Gram Coverage	Mechanism of Action
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Antibiotics classes
Mechanism of Action

1. Aminoglycosides	1. Inhibits Protein Synthesis	P
2. Cephalosporins	2. Inhibits Cell Wall Synthesis	C
3. Tetracyclines	3. Inhibits Protein Synthesis	P
4. Penicillins	4. Inhibits Cell Wall Synthesis	C
5. SulFOnamide	5. Inhibits Folate = Letters Fo	F
6. Fluoro<u>quin</u>olones	6. Inhibits DNA Replication	D
7. Macrolides	7. Inhibits Protein Synthesis	P
8. Carbapenems	8. Inhibits Cell Wall Synthesis	C
9. Lincosamides	9. Inhibits Protein Synthesis	P
10. Glycopeptides	10. Inhibits Cell Wall Synthesis	C

MALT

Macrolides
Aminoglycosides
Lincosamides
Tetracyclines

↓

Inhibits Protein Synthesis

Queen Elizabeth Fears DNA Test Could Damage British Monarchy?

Examples

- Doxy**cycline**
- Mero**penem**
- **Sulfa**methoxazole

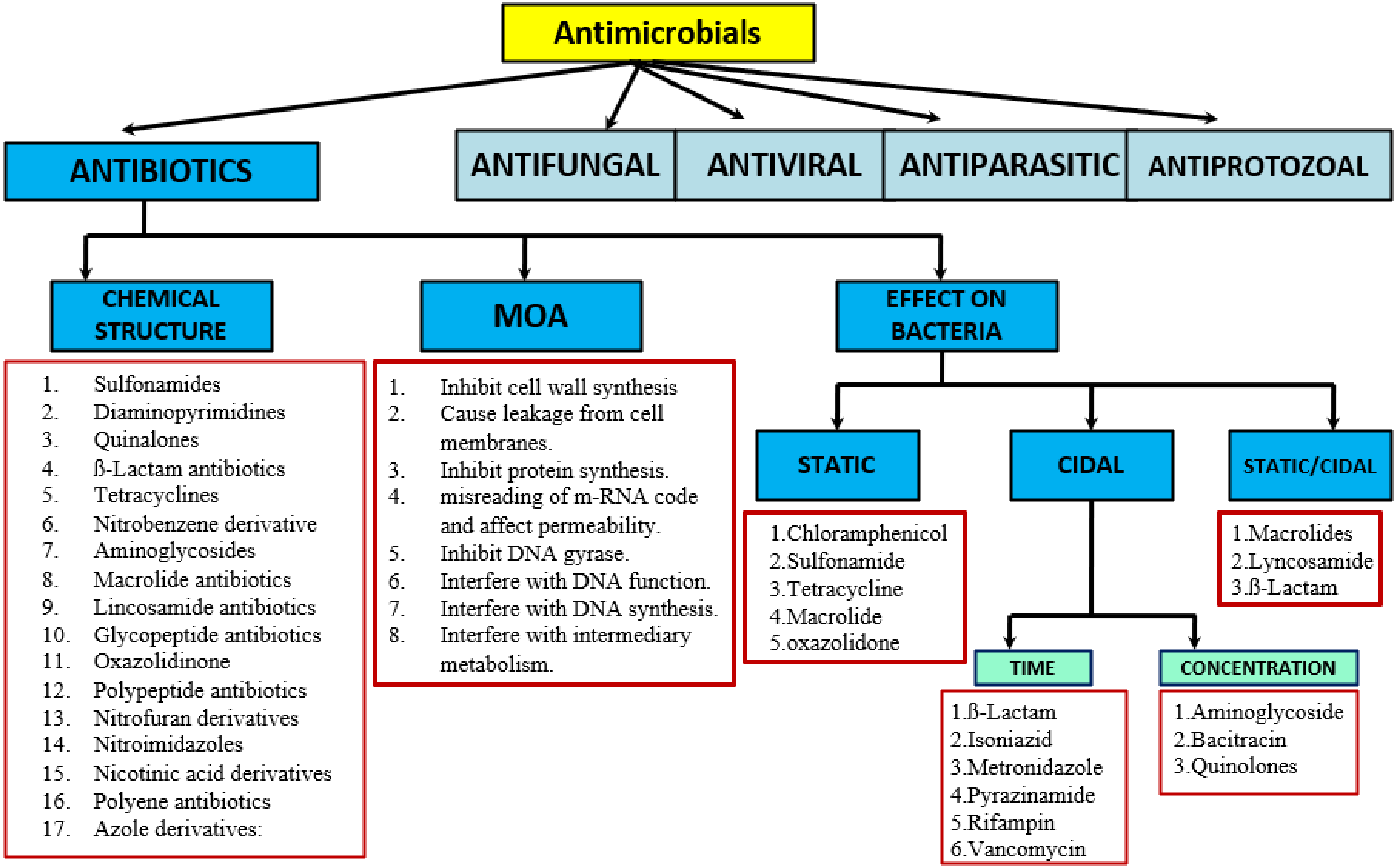
MALT Inhibits Protein Synthesis

GLAM Gram (+) Gram (-)

Mnemonic	Groups	Medication Names	Gram Coverage	Mechanism of Action
Antibiotic				
Can				
Terminate	Tetra**cycline**	Doxy**cycline**	Gram (+)(-)	**Inhibits Protein Synthesis**
Protein				
Synthesis	Sul**FO**namide	**Sulfa**methoxazole	Gram (+)(-)	Inhibits **Fo**late
For				
Microbial				
Cells	**Carbapenem**	Mero**penem**	Gram (+)(-)	**Inhibits Cell Wall Synthesis**
Like				
Germs				

Antibiotic Classes

Antibiotics	Aminoglycosides	Streptomycin Gentamicin	Gram (-)	Inhibit Protein Synthesis (30s)	Bacteremia, Abdominal Infections
Can	Cephalosporins	Ceftriaxone Cefepime	Gram (+)/(-)	Inhibit Cell Wall Synthesis	Skin, Urinary, Resp. Infections
Terminate	Tetracyclines	Tetracycline Doxycycline	Gram (+)/(-)	Inhibit Protein Synthesis (30s)	Lyme Disease, PID, STIs
Protein	Penicillins	Ampicillin Amoxicillin	Gram (+)/(-)	Inhibit Cell Wall Synthesis	ENT, Skin, Urinary Infections
Synthesis	Sulfonamides	Sulfasalazine Sulfamethoxazole	Gram (+)/(-)	Inhibit Folate Synthesis	UTIs, Burns, Eye Infections
For	Fluoroquinolones	Ciprofloxacin Levofloxacin	Gram (+)/(-)	Inhibit DNA Replication	Respiratory & Urinary Infections
Microbial	Macrolides	Azithromycin Erythromycin	Gram (+)	Inhibit Protein Synthesis (50s)	Pneumonia, Sinus, ENT, STIs
Cells	Carbapenems	Meropenem Ertapenem	Gram (+)/(-)	Inhibit Cell Wall Synthesis	Urinary, Abdom. Infections
Like	Lincosamides	Clindamycin	Gram (+)	Inhibit Protein Synthesis (50s)	Skin, Bone, Lung Infections
Germs	Glycopeptides	Vancomycin	Gram (+)	Inhibit Cell Wall Synthesis	MRSA, Skin, Endocarditis



Antimicrobials
ANTIBIOTICS
ANTIFUNGAL
ANTIVIRAL
ANTIPARASITIC
ANTIPROTOZOAL
CHEMICAL STRUCTURE
MOA
EFFECT ON BACTERIA
1. Sulfonamides
2. Diaminopyrimidines
3. Quinalones
4. ß-Lactam antibiotics
5. Tetracyclines
6. Nitrobenzene derivative
7. Aminoglycosides
8. Macrolide antibiotics
9. Lincosamide antibiotics
10. Glycopeptide antibiotics
11. Oxazolidinone
12. Polypeptide antibiotics
13. Nitrofuran derivatives
14. Nitroimidazoles
15. Nicotinic acid derivatives
16. Polyene antibiotics
17. Azole derivatives:
1. Inhibit cell wall synthesis
2. Cause leakage from cell membranes.
3. Inhibit protein synthesis.
4. misreading of m-RNA code and affect permeability.
5. Inhibit DNA gyrase.
6. Interfere with DNA function.
7. Interfere with DNA synthesis.
8. Interfere with intermediary metabolism.
STATIC
CIDAL
STATIC/CIDAL
1.Chloramphenicol
2.Sulfonamide
3.Tetracycline
4.Macrolide
5.oxazolidone
1.Macrolides
2.Lyncosamide
3.ß-Lactam
TIME
CONCENTRATION
1.ß-Lactam
2.Isoniazid
3.Metronidazole
4.Pyrazinamide
5.Rifampin
6.Vancomycin
1.Aminoglycoside
2.Bacitracin
3.Quinolones