Pharmacology Of Antimicrobial Drugs

- **Antiseptics disinfectants**
- **Antibiotics**

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Medicines with an antimicrobial activity are divided into two groups:

1. Non-selective –antiseptics and disinfectants

1. Selective antimicrobial drugs – antibiotics, synthetic antibacterial drugs, antiprotozoal, antiviral, antifungal agents

Germicides

ANTISEPTICS

DISINFEC

ANTISEPTICS:- **(Anti=** against; **septicas** – emitting a fetid smell)

- Chemical substances which are used to destroy, inhibit pathogenic bacteria (not the spores) **on animate (living) surface** such as skin, eye, mucous membranes(as in mouth washes).
- 1879- Lister- **Father of 'Antiseptic surgery'**
- They falls under " **Drug Control Agency of the Government**"

DISINFECTANTS

- Chemical substances or germicides which are use to destroy or inhibit the growth of pathogenic vegetative bacteria (not their spores) on ***inanimate(non-living) surface*** such as glassware's or surgical instruments.

e.g.- Formaldehyde, phenol, ethyl alcohol, soaps.

- They falls under "**Control of Environmental protection agency of the Government**"

- They process "**concentration dependent killing**"
- Antiseptics & Disinfectant are often added to easily available every day utilities like soaps,toothpastes,mouth wash, after saving lotion.

Antiseptics disinfectants mechanisms of action

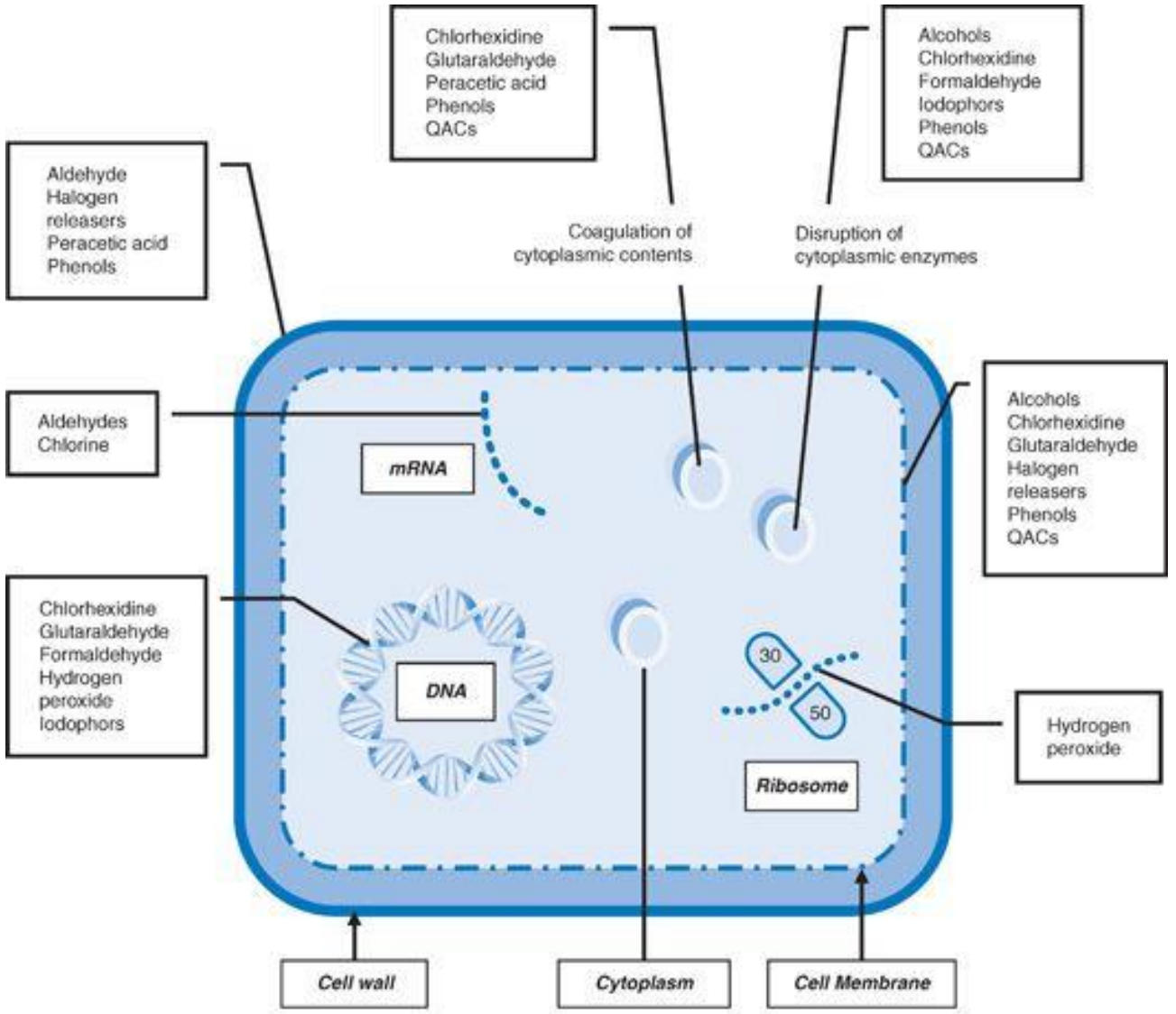


Figure 12.1 ■ **Cellular targets of biocidal agents.** (Adapted from Fanning S. Altered tolerance to biocides: links to antibiotic resistance? Paper presented at: International Association of Food Protection (IAFP), European Symposium on Food Safety; 2011; The Netherlands. http://www.foodprotection.org/events/european-symposia/11Ede/Fanning.pdf. Accessed November 15, 2012.)

Antiseptics and disinfectants

- **Detergents:**
  Cerigel Roccal Degmecid Green soap
- **Nitrofuranes:**
  Furacillin Furaplast Lifuzol Clefurin
- **Biguanides:**
  Chlorhexidine
- **Phenols and related compounds:**
  Phenol Rezorcine Ferezol Trikrezol
- **Dyes:**
  Methylene blue Brilliant green Aethacridine lactate
- **Halogens and halogen containing compounds:**

  Chlorine:
  Chloramine B Chlorhexidine Pantothenatecide

  Iodine:

  Iodine alcohol solution Lugol solution Iodophore Iodinole
- **Oxidizing agents:**

  Hydrogen peroxide Potassium permanganate Hydroperite
- **Aldehydes and Alcohols:**

  Formaldehyde Lizoform Hexamethylene tetramine Ethanol

Antiseptics and disinfectants

9. Heavy metals:

Mercury: Mercury bichloride

Mercury monochloride Lead plaster

Silver: Silver nitrate

Protargole Collargole

Zinc: Zinc sulfate

Bismuth: Xeroform Dermatol

10. Acids and alkalis:

Boric acid Salicylic acid Benzoic acid

Solutio Ammonii caustici 10%

10. Mineral oil, synthetic balms, preparations of sulfur and pitch:

Pitch (Pix liquide)

Naphthalan ointment

Viniline

11. Natural preparations:

Sodium uncinate

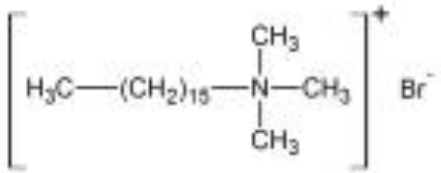
Evcalimin Marigolds bloom

(Flores Calendulae officinalis)

Tinctire Saphorae yaponicae

Requirements for antiseptics and disinfectants

- ✓ Must have a broad spectrum of activity
- ✓ Rapid onset of action
- ✓ Should have a small latent period
- ✓ Should have a high activity
- ✓ Must be chemically resistant
- ✓ High availability and cost
- ✓ Luck of local irritant or allergic effect on tissues
- ✓ Minimal absorption from place of application
- ✓ Low toxicity



Cetyltrimethylammoniumbromide

Detergents

- **Detergents** - a substances with a high surface activity.
- Show antiseptic and cleansing action.
- Distinguish anionic and cationic **detergents**.
- **Anionic detergents** include ordinary soaps (**sodium or potassium salts** of fatty acids).
- As antiseptics mainly used cationic surfactants: **benzalkonium chloride, cetylpyridinium chloride, miramistim**.
- **Benzalkonium chloride** has antibacterial, antiprotozoal and spermicidal action (spermicidal effect develops in two stages: first - the destruction of the flagellum, and then - the gap of the sperm head, which makes it impossible to fertilization).
- Used for treatment of skin, mucous membranes, wounds, rinsing the bladder, urethra, and for contraception in women.

Nitrofuran derivatives (furacillin, furazolidone)

- **Spectrum of action:** Gr-, Gr + bacteria (staphylococci, streptococci, dysentery bacillus, intestinal coli, Salmonella paratyphi, the causative agent of gas gangrene, etc.) and protozoa (Trichomonas, Giardia).
- **Pharmacodynamic:** influenced microbes reductase, there is a restoration of the nitro group and their transformation into toxic products for cells (inhibition of the respiratory chain, the destruction of the microbial wall).
- In the presence of pus does not lose effectiveness.
- **Apply** for external treatment of wounds, skin, mucous membranes, wash serous and joint cavities, otitis media, conjunctivitis and others. Eye diseases and orally for the treatment of bacterial dysentery.

Group of dyes

Ethacridine lactate (rivanol), Brilliant green, Methylene blue

- Antimicrobial activity of this group **falls In the protein environment**
- The most sensitive **Gr + bacteria**, **cocci**.

Ethacridine lactate (rivanol):

- used in surgery, gynecology, urology, ophthalmology, dermatology. For washing of fresh and infected wounds, cavities (pleura, peritoneum), bladder, uterus.

Brilliant green (1-2% water and alcohol sol.):

- for the treatment of skin with scratches, pyoderma, blepharitis, and others.

Methylene blue:

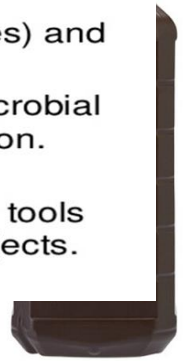
- used internally for urinary tract infections (cystitis, urethritis).
- I/V 1% sol. 50-100 ml in case of **poisoning with hydrocyanic acid or salts (in large doses translates hemoglobin to methemoglobin which comes into contact with a non-toxic form of cyanide complex cyanmethemoglobin).**
- When administered I/V in small doses (0.1-0.15 ml/kg 1% sol.) contrary methylene blue restores methemoglobin in the hemoglobin **(with nitrite poisoning, aniline, and others.)**

Group of aldehydes and alcohols

- PREPARATIONS: FORMALDEHYDE SOLUTION, LIZOFORM, ETHYL ALCOHOL, HEXAMETHYLENETETRAMINE (METHENAMINE)

Formaldehyde solution (Formalin)

- Has antimicrobial (vegetative forms and spores) and deodorizing effects.
- MECHANISM OF ACTION: dehydration of microbial cells protoplasm proteins causing its destruction.
- Is used as a disinfectant and deodorant, skin treatment with sweating (0.5-1%), disinfection tools (0.5%). For the preservation of anatomical objects.



HYDROGEN PEROXIDE:

- **Mode of action:** It acts on the microorganisms through its release of nascent oxygen. Hydrogen peroxide produces hydroxyl-free radical that damages proteins and DNA.
- **Application:** It is used at 6% concentration to decontaminate the instruments, equipments such as ventilators. 3%.Hydrogen Peroxide Solution is used for skin disinfection and deodorising wounds and ulcers. Strong solutions are sporicidal.
- **Disadvantages:** Decomposes in light, broken down by catalase, proteinaceous organic matter drastically reduces its activity.

$KMnO_4$

- Strong Oxidizing agent, liberates Oxygen when comes in contact with organic matter or bacteria
- Strong antibacterial activity
- Astringent, caustic, deodorant
- 1:3,000 is less irritant
- 1:1000 solutions are used for douching, irrigating cavities and cleansing wounds
- A 0.02% soln. is used as gastric lavage in poisoning
- A 5% soln. is used as astringent

Biguanides

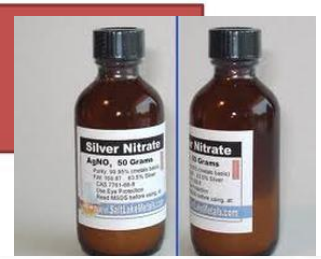
Chlorhexidine: (Savlon)

- Acts by disrupting bacterial cell membrane & denaturation of bacterial proteins
- Non irritant ,more active against gram +ve bacteria.
- Used in for surgical scrub, neonatal bath, mouth wash & general skin antiseptic.
- Most widely used antiseptic in dentisry 0.12-0.2% oral rinse or 0.5 -1 % tooth paste

Iodophores

- Known as povidine iodine.
- Non toxic, non staining prolonged action.
- Used on
  boils, furunculosis, burns, ulcers, tinea, surgica l srub, disinfecting surgical instruments, non specific vaginitis.

Metallic salts



SILVER COMPOUNDS

Prophylactic environmental effect. Silver NPs are added into antibacterial. paints and disinfectants to ensure an aseptic environment for the patient.

Prophylactic antibacterial effect. Silver NPs are added as a surface coating for neurosurgical shunts and venous catheters.

Prophylactic antibacterial effect. Silver NPs are added to bone cement and other implants.

Infection protection. Silver-NP-impregnated wound dressings prevent infection and enhance wound healing.

Cauterization. Silver nitrate used to stop epistaxis.

Antibacterial effect. First medical use: Crede's 1% silver nitrate eyedrops were used to prevent mother-to-child transmission of gonococcal eye infection.

Inflammatory effect (causes deliberate adhesion). Silver nitrate is used in pleurodesis.

Regenerative effect. Silver sulfadiazine cream is used as a dressing for burns and ulcers. It also improves skin re-generation.

Cauterization. Silver nitrate is used to stop the growth of post-traumatic granulomas, or 'wild flesh'.

ANTIBIOTICS - substances derived from microorganisms or produced synthetically, that destroys or limits the growth of a living organisms

Classification according to:

1. **Sourses:** - **Natural** a.Fungi (penicillin)

   b. Bacteria (polymixin, tetracycline, chloramphenicol)

   -Semi-syntetics

2. **Antimicrobial activity:** -bactericidal - bacteriostatic

3. **Spectrum of activity:** - narrow spectrum - broad spectrum

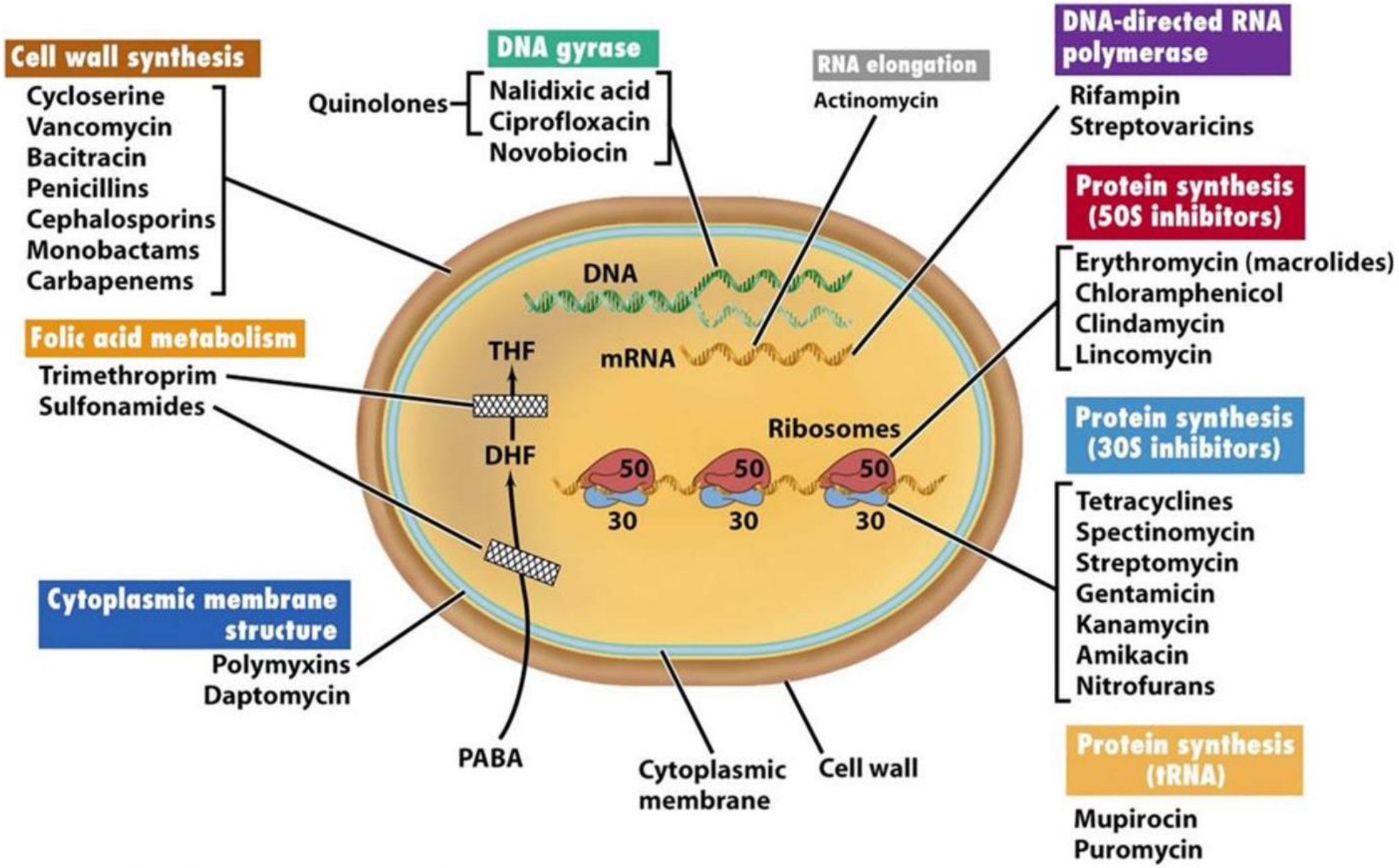
- **4. Mechanism of action:** a. inhibition of cell wall synthesis

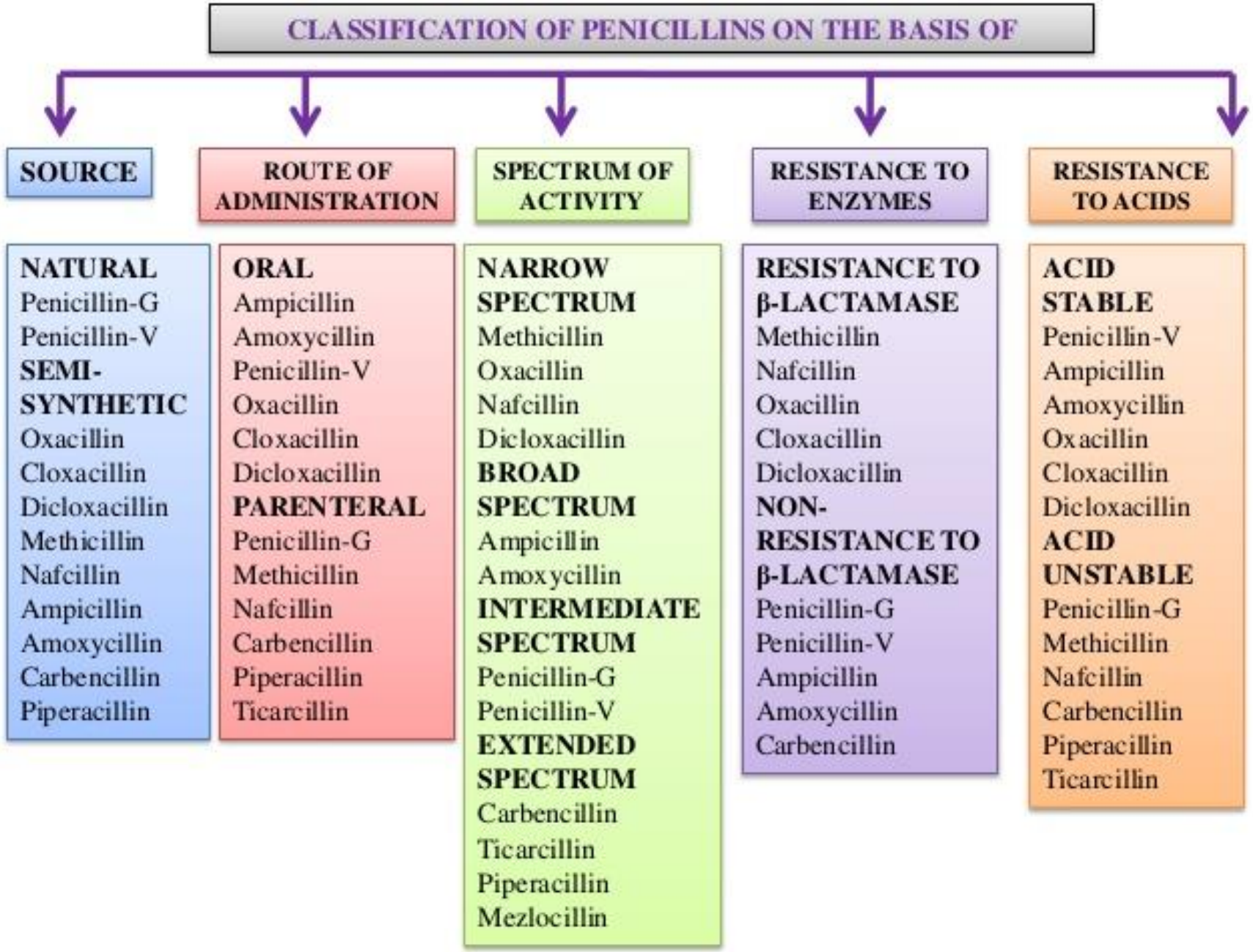
  b. Alteration of cell membrane permeability

  c. Inhibition of bacterial protein synthesis

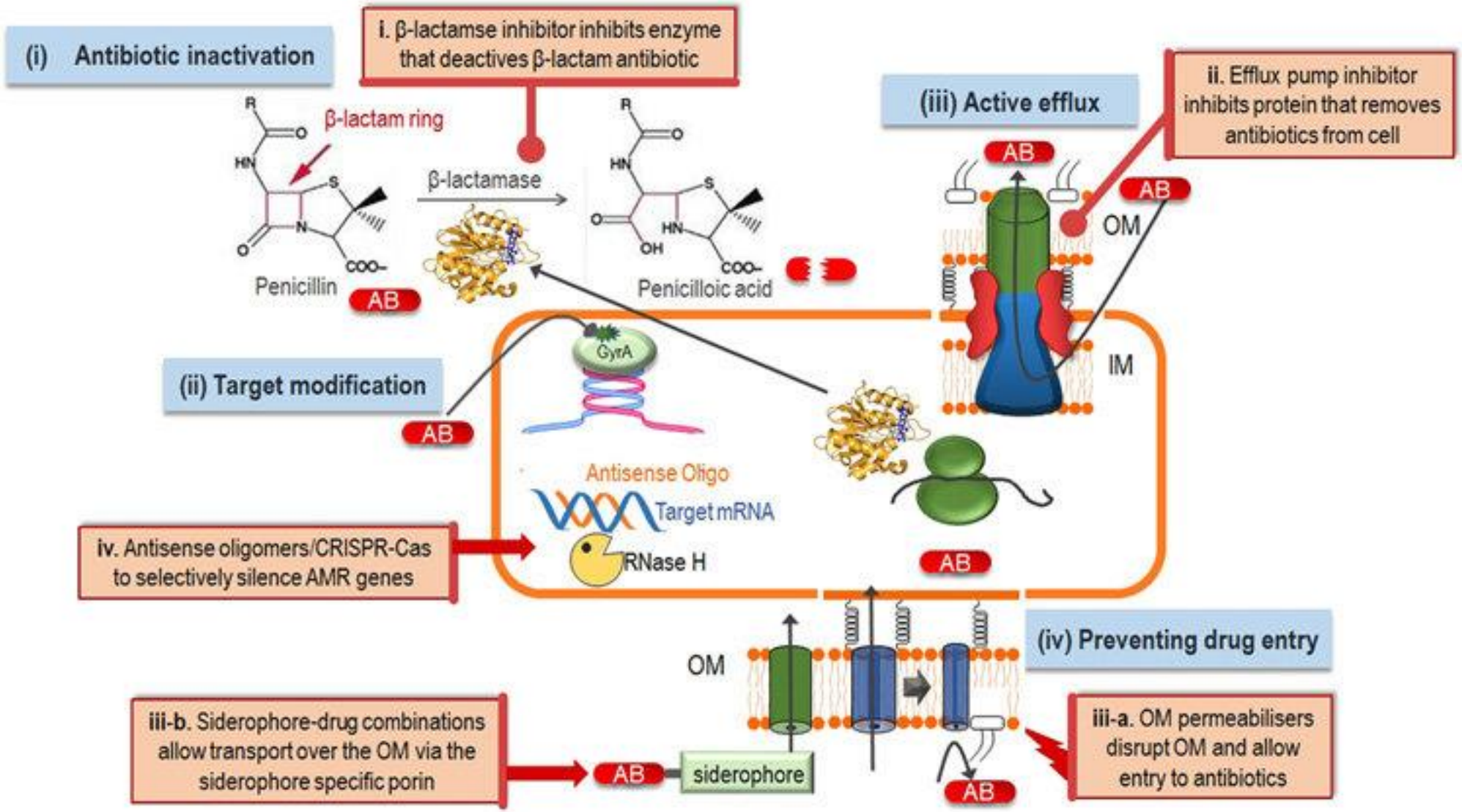
  d. Inhibition of nucleic acid synthesis

CLASSIFICATION OF ANTIBIOTICS BY MECHANISM OF ACTION




CLASSIFICATION OF PENICILLINS ON THE BASIS OF
SOURCE
NATURAL
Penicillin-G
Penicillin-V
SEMI-SYNTHETIC
Oxacillin
Cloxacillin
Dicloxacillin
Methicillin
Nafcillin
Ampicillin
Amoxycillin
Carbencillin
Piperacillin
ROUTE OF ADMINISTRATION
ORAL
Ampicillin
Amoxycillin
Penicillin-V
Oxacillin
Cloxacillin
Dicloxacillin
PARENTERAL
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin
SPECTRUM OF ACTIVITY
NARROW SPECTRUM
Methicillin
Oxacillin
Nafcillin
Dicloxacillin
BROAD SPECTRUM
Ampicillin
Amoxycillin
INTERMEDIATE SPECTRUM
Penicillin-G
Penicillin-V
EXTENDED SPECTRUM
Carbencillin
Ticarcillin
Piperacillin
Mezlocillin
RESISTANCE TO ENZYMES
RESISTANCE TO β-LACTAMASE
Methicillin
Nafcillin
Oxacillin
Cloxacillin
Dicloxacillin
NON-RESISTANCE TO β-LACTAMASE
Penicillin-G
Penicillin-V
Ampicillin
Amoxycillin
Carbencillin
RESISTANCE TO ACIDS
ACID STABLE
Penicillin-V
Ampicillin
Amoxycillin
Oxacillin
Cloxacillin
Dicloxacillin
ACID UNSTABLE
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin

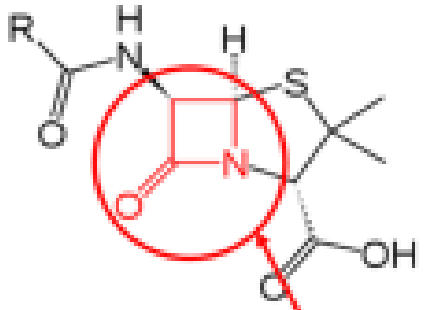
ANTIMICROBIAL RESISTANCE

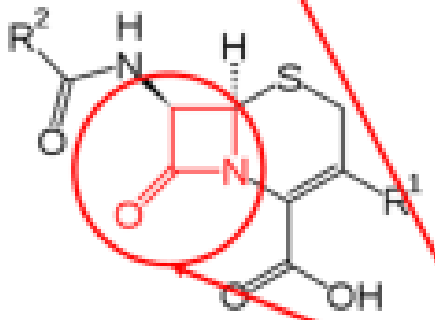


Antibiotics inhibiting cell wall synthesis

B-lactams

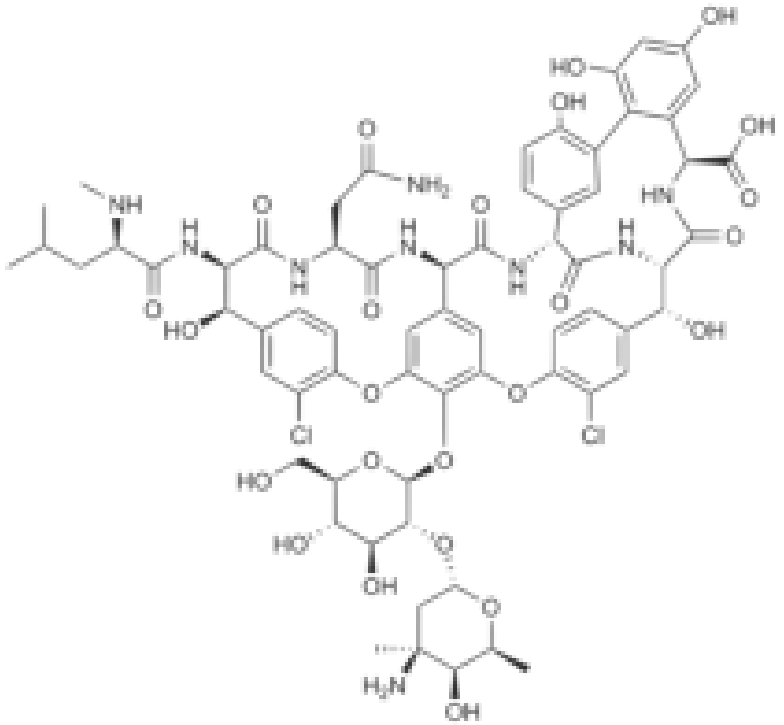
- Penicillin's
- Cephalosporin's
- Carbapenems
- Monobactams



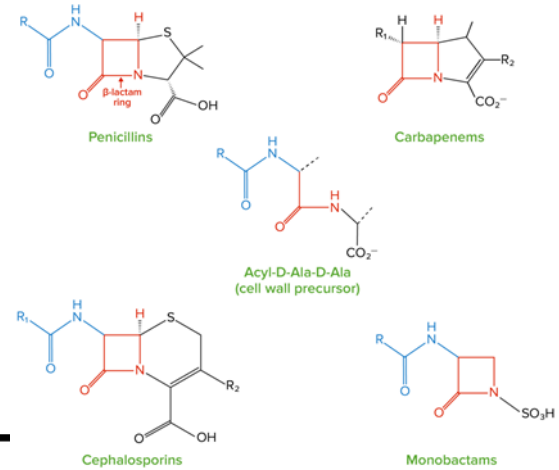


β-. Lactam ring

glycopeptides



Beta Lactams



Penicillins

PCN

Penicillin G
Benzathine PCN
VK PCN (PO)

Anti-Staph

Oxacillin (IV)
Nafcillin (IV)
Dicloxicillin (PO)

Amino-PCN

Amp +/-
Sulb (IV) #
Amox +/-
Clav (PO) #

Anti-Pseud

Pip +/- Tazo ^ #
Tic +/- Clav ^ #
(not available)

Cephalosporins

1. Cephalexin
   Cefazolin
2. Cefuroxime
3. Ceftriaxone
   Ceftazidime ^
4. Cefepime ^

---

5. Ceftaroline
   (Like CTX+MRSA)

Increasing gram neg coverage

Extended GNR

Ceftol-Tazo * ^ ~
Ceftaz-Avi * ^ ~

Monobactam

Aztreonam ^

- Aerobic Gram neg
- Pseudomonas
- Bad 4 gram pos
- Bad 4 anaerobes

KEY
* ESBL
^ Pseudomonas
~ Carbapenem-R
# Anaerobes

Carbapenems

Imipenem * ^ #

Meropenem * ^ #
+/- vaborbactam ~

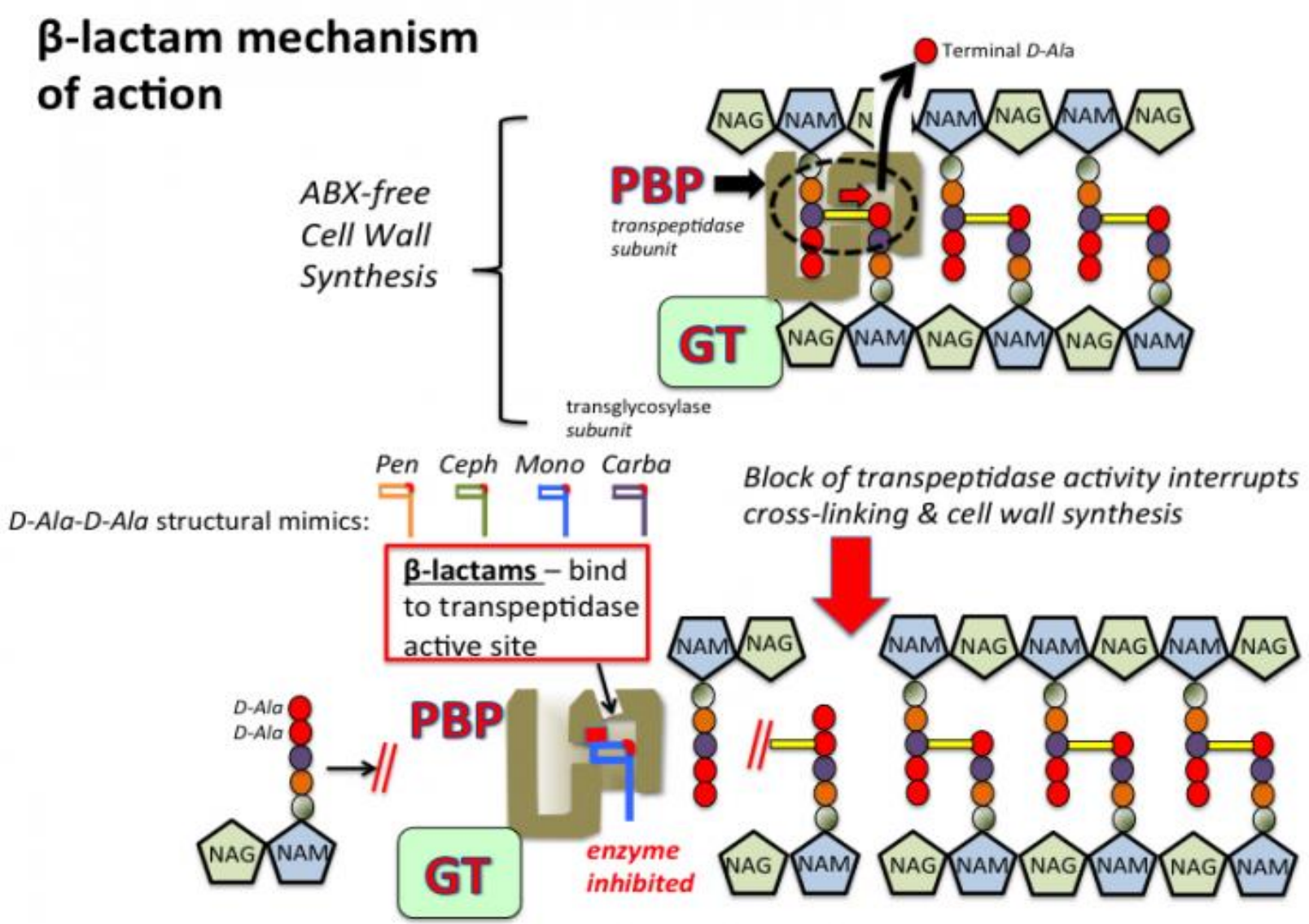
Doripenem * ^ #

[Ertapenem] * #

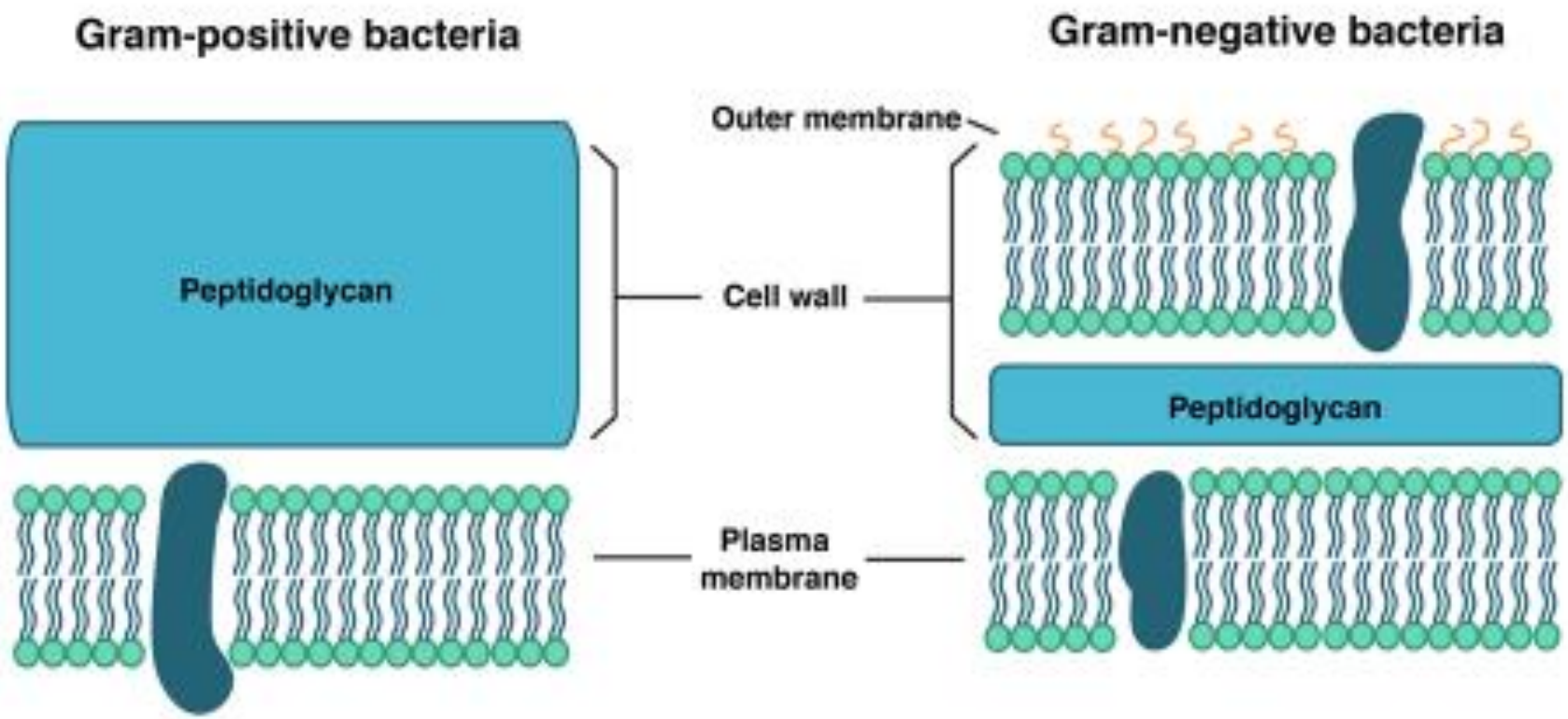
- No pseudomonas
- 1x daily dosing

D. Serota 2018

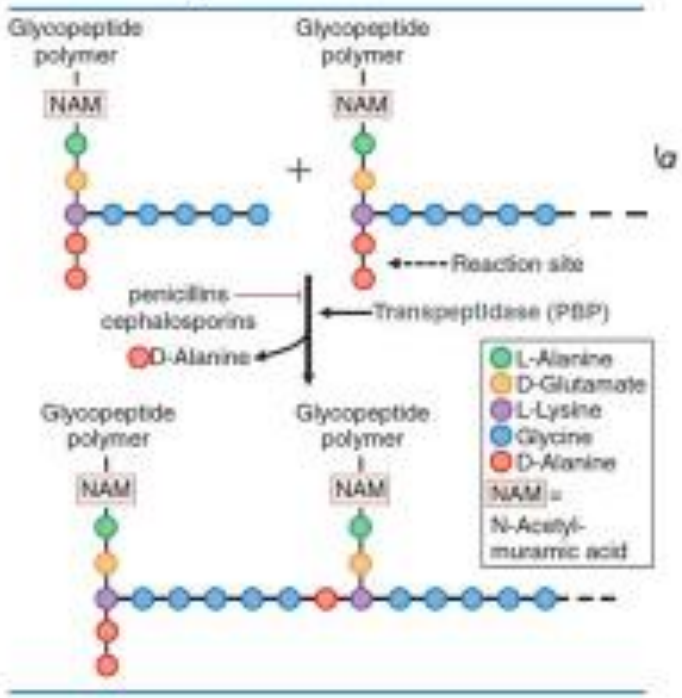
Penicillins, like all β-lactam antibiotics, inhibit bacterial growth by interfering with the transpeptidation reaction of bacterial cell wall synthesis



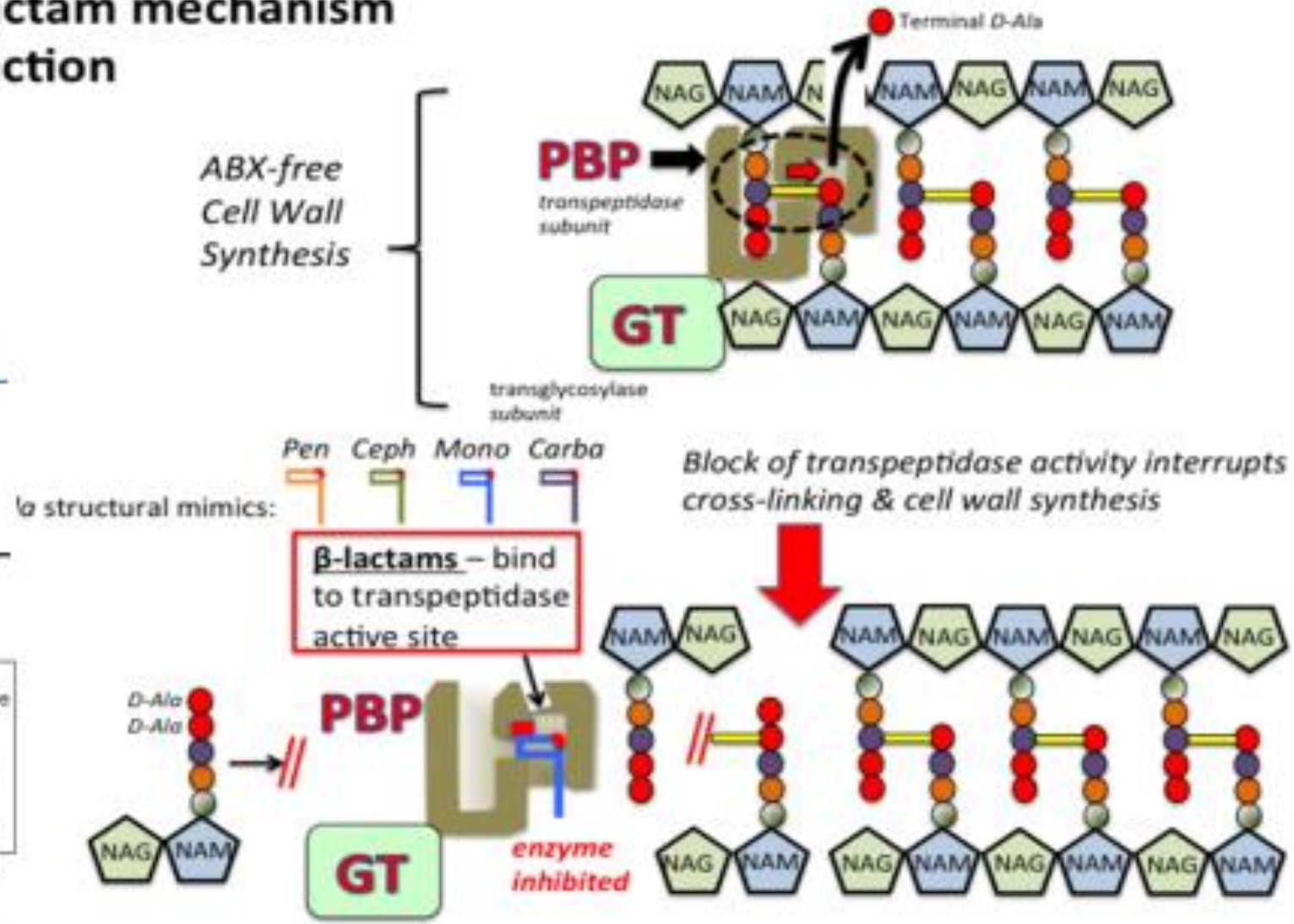
Bacterial cell wall. Structure



β-lactams inhibit bacterial growth by interfering with the transpeptidation reaction of bacterial cell wall synthesis

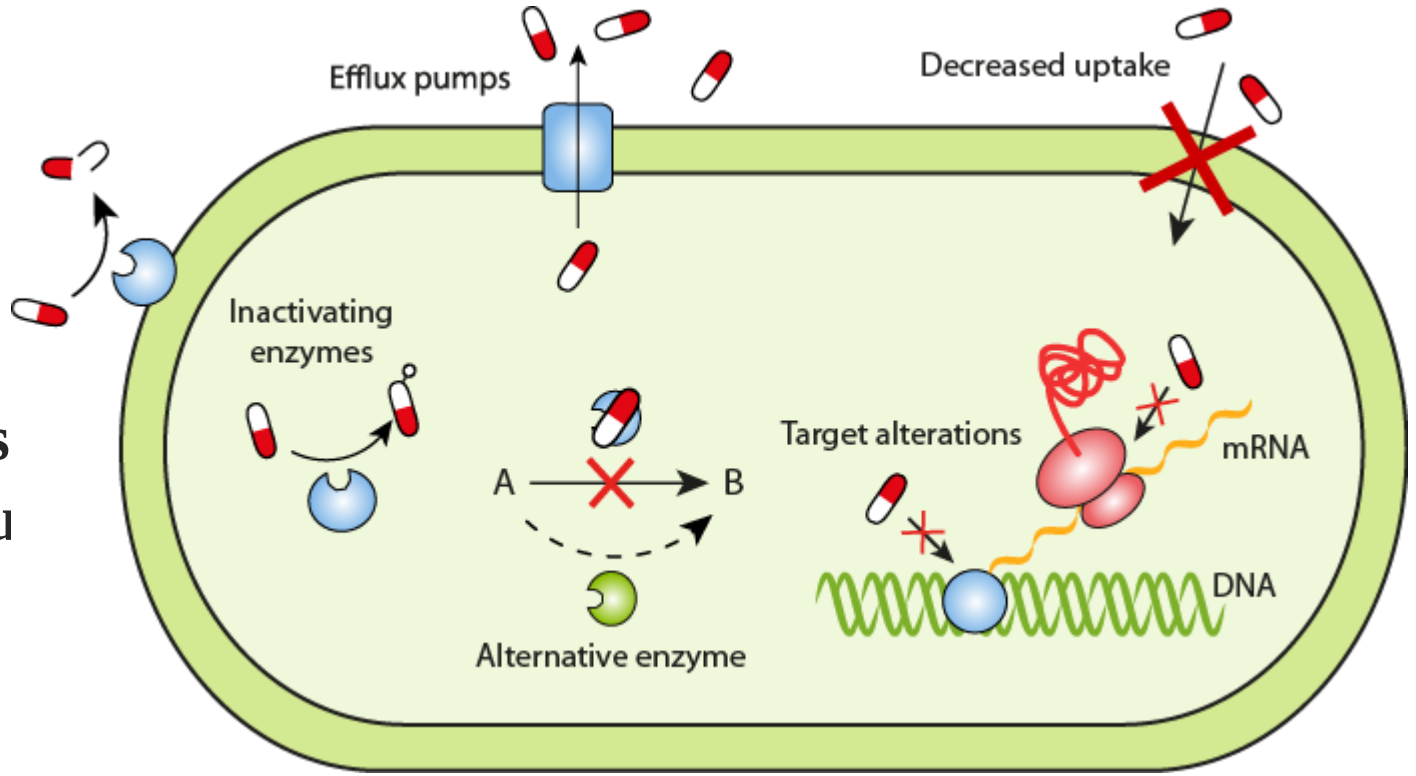


β-lactam mechanism of action

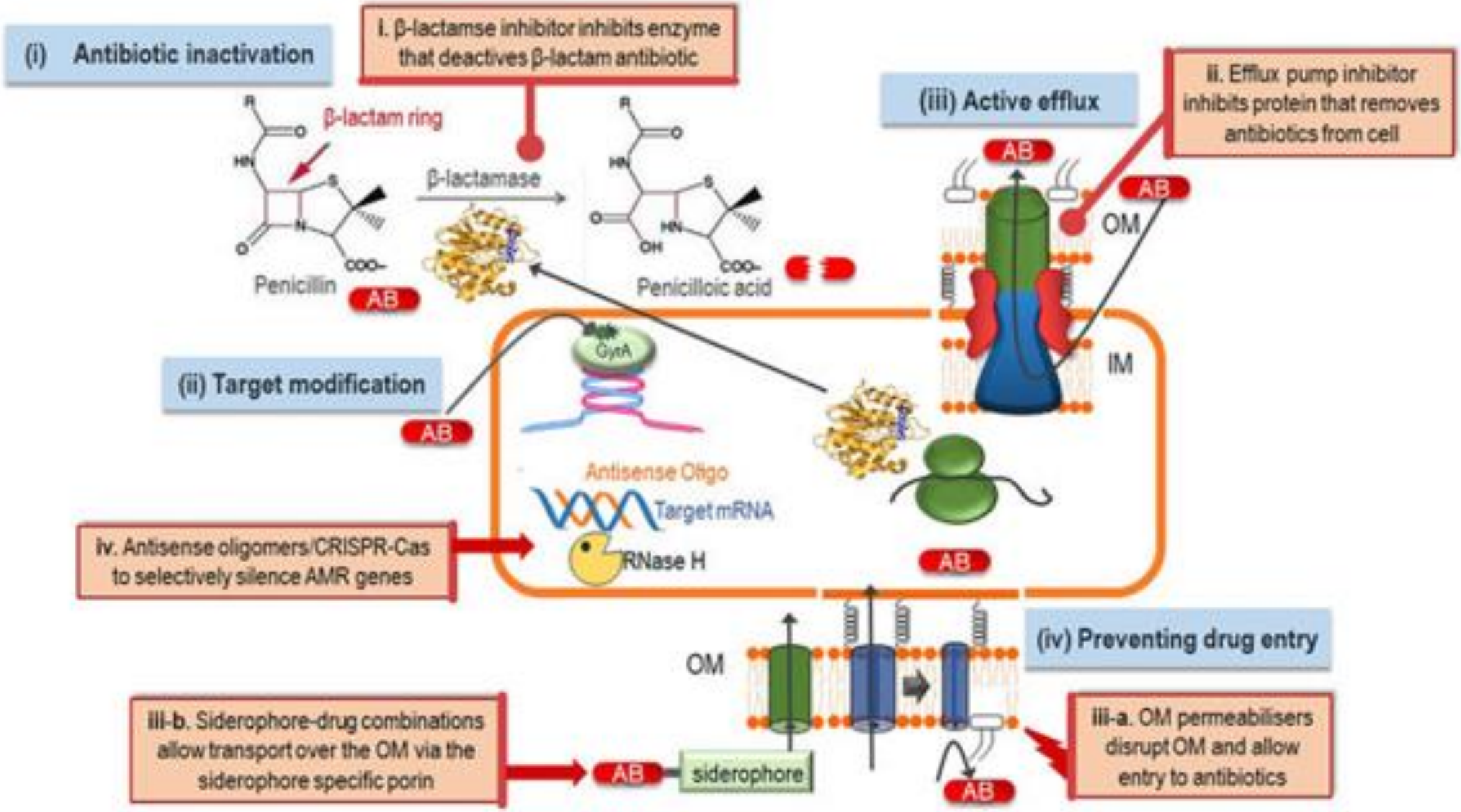


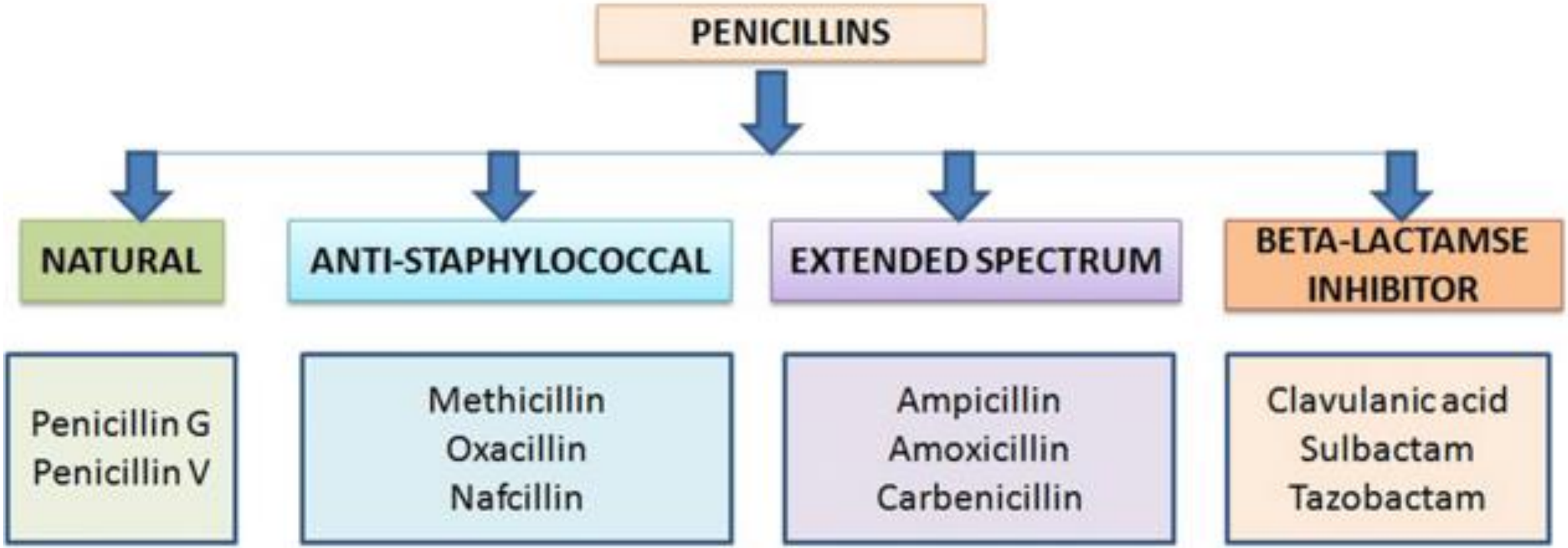
Resistance Resistance to penicillins and other β-lactams

- (1) **inactivation of antibiotic by β lactamase**
- **(2) modification of target PBPs**
- **(3) impaired penetration of dru to target PBPs**
- **(4) antibiotic efflux**



Betalactamase production is the most common mechanism of resistance. Hundreds of different β-lactamases have been identified. Some, such as those produced by Staphylococcus aureus, Haemophilus influenzae, and Escherichia coli, are relatively narrow in substrate specificity, preferring penicillins to cephalosporins. Other β-lactamases, eg, AmpC βlactamase produced by Pseudomonas aeruginosa and Enterobacter sp, and extended–spectrum β-lactamases (ESBLs), hydrolyze both cephalosporins and penicillins. Carbapenems are highly resistant to hydrolysis by penicillinases and cephalosporinases, but they are hydrolyzed by metallo-β lactamase and carbapenemases.


(i) Antibiotic inactivation
I. β-lactamse inhibitor inhibits enzyme that deactives β-lactam antibiotic
β-lactam ring
β-lactamase
Penicillin
Penicilloic acid
AB
(iii) Active efflux
ii. Efflux pump inhibitor inhibits protein that removes antibiotics from cell
OM
IM
(ii) Target modification
GyrA
Antisense Oligo
Target mRNA
RNase H
iv. Antisense oligomers/CRISPR-Cas to selectively silence AMR genes
(iv) Preventing drug entry
iii-b. Siderophore-drug combinations allow transport over the OM via the siderophore specific porin
siderophore
iii-a. OM permeabilisers disrupt OM and allow entry to antibiotics


PENICILLINS
NATURAL
ANTI-STAPHYLOCOCCAL
EXTENDED SPECTRUM
BETA-LACTAMSE INHIBITOR
Penicillin G
Penicillin V
Methicillin
Oxacillin
Nafcillin
Ampicillin
Amoxicillin
Carbenicillin
Clavulanic acid
Sulbactam
Tazobactam

Penicillins

BIOSYNTHETIC PENICILLINS

1. For parenteral uses

- *Short acted drugs:*

Benzylpenicillin - sodium

Benzylpenicillin - potassium

- *Long acted drug*

Procaine benzylpenicillin

Bicillin-1 Bicillin-5

2. For enteral uses

Phenoxymethylpenicillin

SEMISYNTHETIC PENICILLINS

- Penicillinase-resistant antistaphyllococcial

Oxacillin Nafcillin Cloxacillin Dicloxacillin

- Extended-spectrum amino-penicillins

Ampicillin Amoxicillin

- Antipsevdomonadal penicillins:

Carboxypenicillins: Carbenicillin Tikarcillin

Ureidopenicillins: Azlocillin Mezlocillin Piperacillin

Combined preparations

- **Ampiox (ampicillin, oxacillin)**
- **Unazin (ampicillin, sulbactam)**
- **Augmentin (Amoxicillin,clavulanic acid)**
- **Tazocin (piperacillin, tazobactam)**

Clavulanic acid, sulbactam, tazobactam - inhibitors beta-lactamases (penicillinases) are often used in combination with penicillins to prevent their inactivation.

Penicillins

- **Mechanism of Action:**
  - **Inhibits bacterial cell wall synthesis by binding and inactivating proteins (penicillin binding proteins)** present in the bacterial cell wall.
  - Penicillins **inhibit the transpeptidation reaction** and **block cross-linking of the cell wall**. This results in lysis of the cell wall due to high internal osmotic pressure.
  - **Penicillins are only effective against growing bacteria**, because in non-growing cells, the process of cross-linking does not occur, and penicillins will have no effect.
    - Hence when bacteria are in a stationary phase of growth due to nutrient depletion or the presence of toxic products, penicillins will be relatively ineffective (because few cells are dividing). They are most effective during the logarithmic phase of rapid cell division.
  - Inactivation of the **inhibitor of autolysins** within the cell also contributes to cell lysis.
  - Little activity against gram-negative rods because penicillin can't penetrate their outer membrane.
  - Greatest activity against **gram-positive organisms**, **gram-negative cocci** (which lack an outer membrane), and **non-beta-lactamase producing anaerobes**.

Spectrum antimicrobial activity of penicillin's

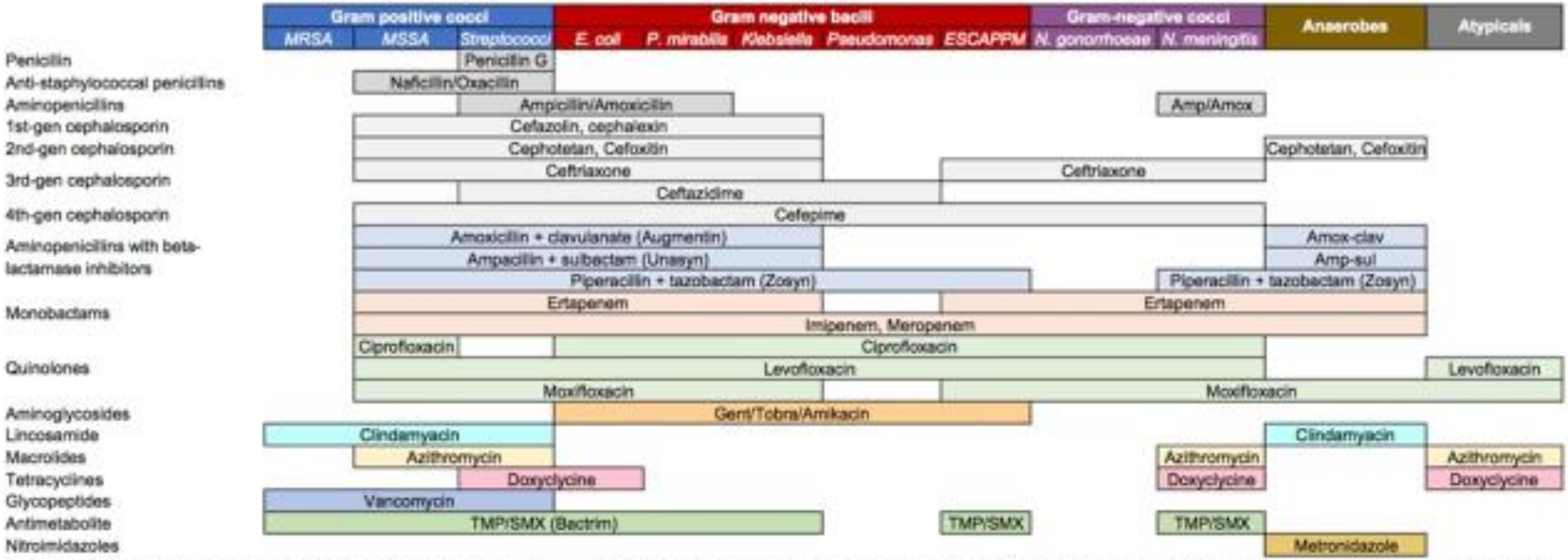
Greatest activity against **gram-positive organisms**, **gram-negative cocci** (which lack an outer membrane), and **non-beta-lactamase producing anaerobes**.

Gram positive cocci & rods

- ***Streptococcus Grp A & B***
- *Streptococcus viridans*
- *Enterococcus*
- *Listeria monocytogenes*
- ***Actinomyces***

- **Gram positive anaerobes**
  - ***Peptostreptococcus***
  - ***Clostridium tetani***
  - ***Clostridium perfringens***
  - *Clostridium botulinum*
- **Gram negative cocci**
  - ***Neisseria meningitidis***
  - *Pasteurella multocida*
- Spirochetes
  - ***Treponema pallidum***
  - Leptospirosis

Spectrum of antibacterial activity



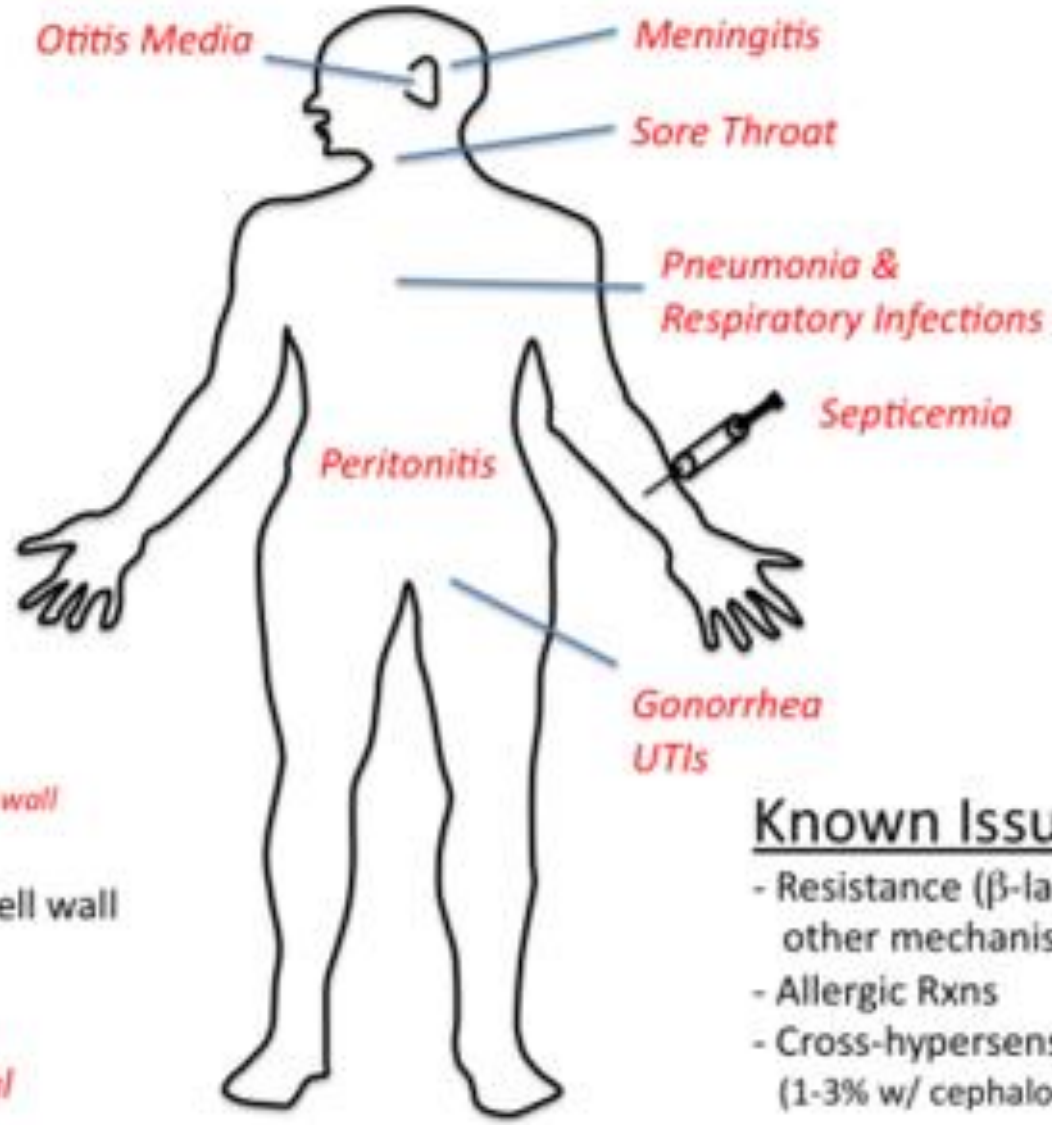
See github.com/aetherist/antibiogram for details. For educational purposes only. TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.

Penicillin Uses

Routes:

oral

i.v.



Mechanism:

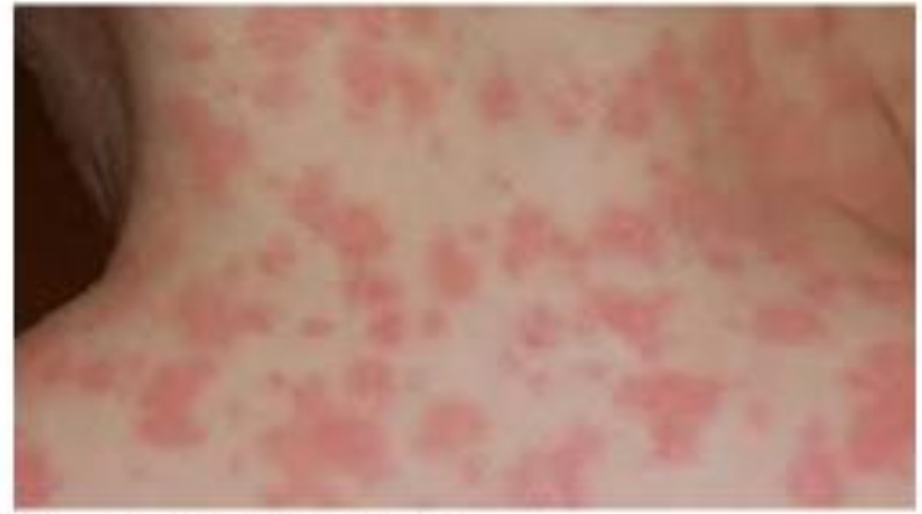
Inhibits transpeptidation of cell wall

bactericidal

Known Issues:

- Resistance (β-lactamase, & other mechanisms)
- Allergic Rxns
- Cross-hypersensitivity (1-3% w/ cephalosporins)

Adverse effects



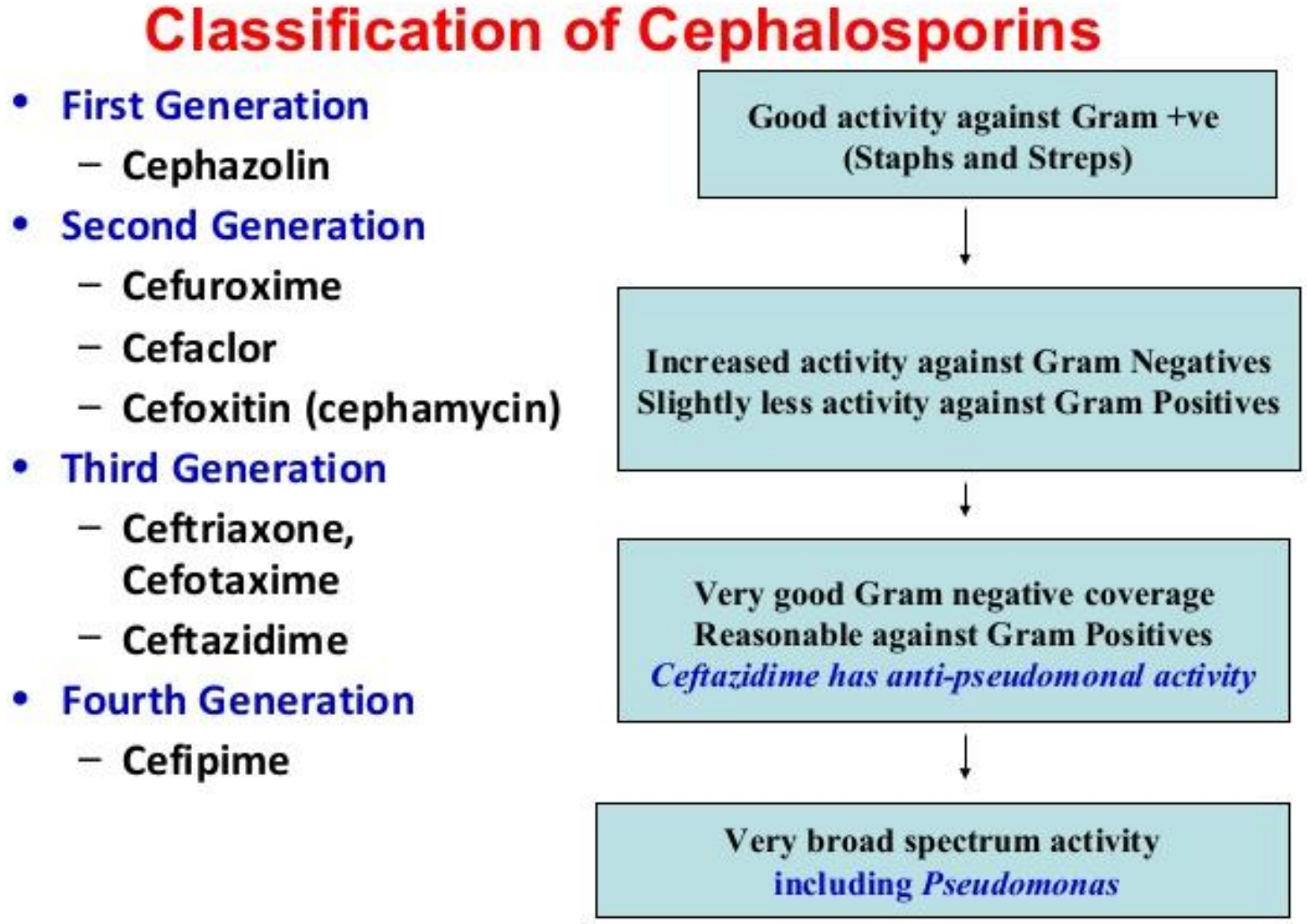
- Hypersensitivity Reactions
  - rash, urticaria, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis and anaphylaxis

- Penicillins and their breakdown products act as haptens after covalent reaction with proteins
  - The most abundant breakdown product is the penicilloyl (major) moiety
- Very high doses of penicillin G can cause seizures in kidney failure
- These are cross-reactions between various types of penicillins.

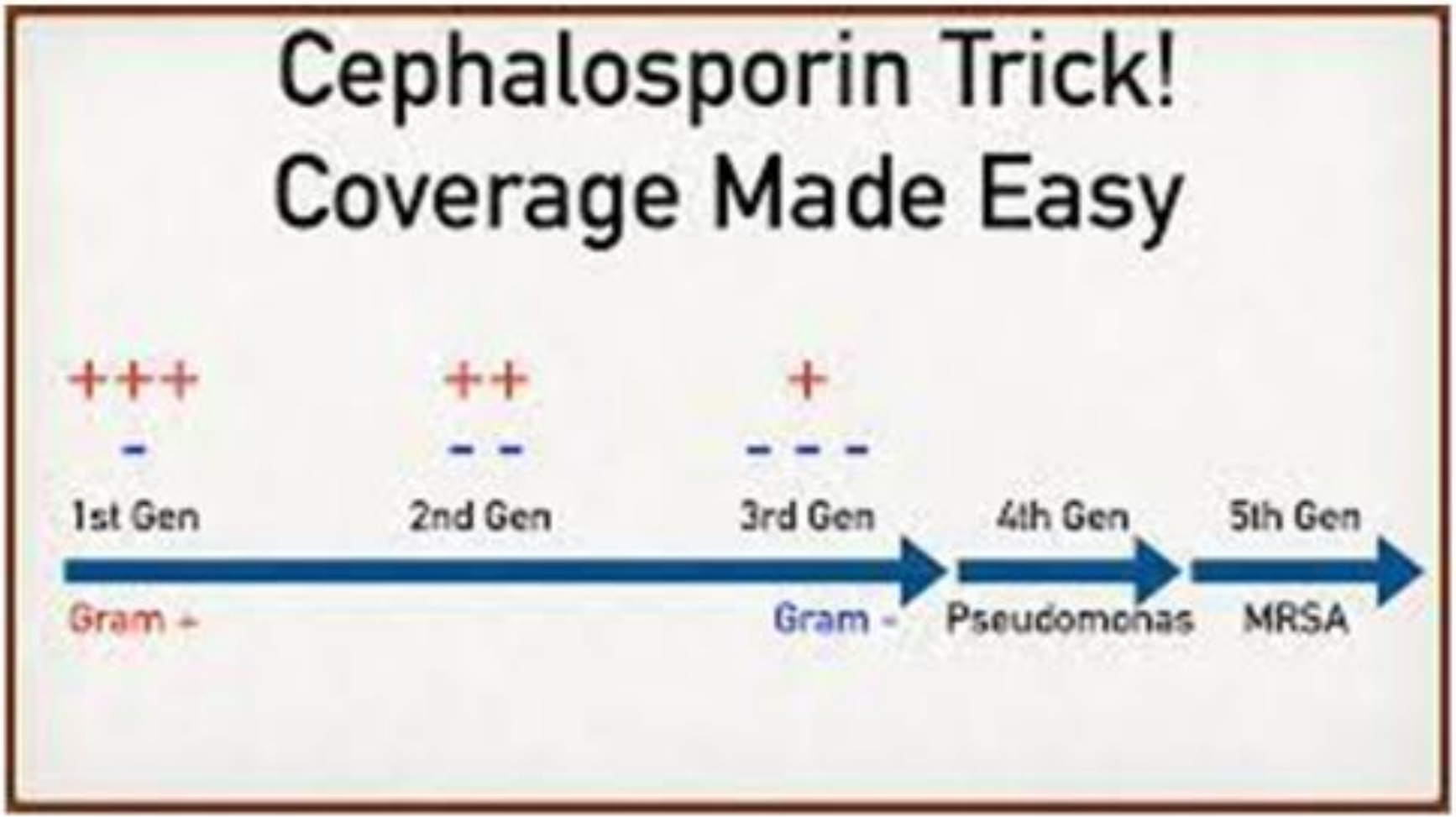
Cephalosporin's

are similar to penicillins but more stable to many bacterial β lactamases and, therefore, have a broader spectrum of activity. However, strains **of E coli** and **Klebsiella** sp expressing extended-spectrum β lactamases that can hydrolyze most cephalosporins are a growing clinical concern. Cephalosporins are not active against L monocytogenes, and of the available cephalosporins, only **ceftaroline** has some activity against enterococci.

Cephalosporins can be classified into four major groups or generations, depending mainly on the spectrum of antimicrobial activity.



Cephalosporin Trick!
Coverage Made Easy



Spectrum of antimicrobial activity of ceralosporines

I поколение:
Гр «+» кокки
(*Staphylococcus spp. Streptococcus spp.*)

- Инфекция кожи и мягких тканей
- Антибиотикопрофилактика в хирургии

II поколение:
Гр «+» кокки, Гр «-» кокки (*Neisseria gonorrhoeae*),
Гр «-» палочки (*H.Influenzae, E. Coli*)

- Инфекции верхних и нижних дыхательных путей
- Инфекции мочевыводящих путей (МВП)

III поколение:
Гр «+» кокки, Гр «-» кокки (*Neisseria spp*),
Гр «-» палочки (*H.Influenzae, E. Coli, Salmonella spp, Shigella spp*)
P. Aeruginosa – **только цефоперазон, цефтобипрол!**
Активны в отношении внутрибольничных штаммов

- Внутри- и внебольничная пневмония
- Тяжелые инфекции МВП
- Тяжелые инфекции кожи и мягких тканей
- Тяжелые инфекции костей и суставов
- Инраабдоминальные инфекции
- Генерализованный сальмонеллез
- Менингит
- Сепсис

IV поколение:
Гр «+» кокки, Гр «-» кокки (*Neisseria spp*),
Гр «-» палочки (*H.Influenzae, E. Coli, Salmonella spp, Shigella spp,*
P. Aeruginosa) ***+ внутрибольничные штаммы***

- Тяжелые внутрибольничные инфекции, вызванные полирезистентной флорой

V поколение:
Цефтобипрол – широкий спектр, но ключевую роль играет активность в отношении **MRSA**!

- Осложненная инфекция кожи и мягких тканей

Cephalosporins Adverse effects

- Allergy (10-20% of patients with penicillin allergy are also allergic to cephalosporins)
- Nephritis and acute renal failure
- Thrombophlebitis
- Superinfections
- Gastrointestinal upsets when given orally

CARBAPENEMS

IMIPENEM MEROPENEM
PRIMAXIN (imipenem + cilastatin)

- **Ultra-broad-spectrum antibiotics (active against many aerobic and anaerobic Gr-positive and Gr-negative organisms)**
- **It is resistant to most β lactamases but not carbapenemases or metallo-β lactamases. Enterococcus faecium , methicillin-resistant strains of staphylococci, Clostridium difficile, Burkholderia cepacia, and Stenotrophomonas maltophilia are resistant.**
- **Imipenem is inactivated by dehydropeptidases in renal tubules, resulting in low urinary concentrations.**

Imipenem is used with cilastatin, which blocks its breakdown in the kidneys by inhibition of dihydropeptidase enzyme

MONOBACTAMS

AZTREONAM

- **Monobactams are drugs with a monocyclic β-lactam ring (Figure 43–1).**
- **Their spectrum of activity is limited to aerobic gram-negative rods (including P aeruginosa). pseudomonads,**

Neisseria meningitidis,

Hemophilus influenzae

- **Unlike other β-lactam antibiotics, they have no activity against gram-positive bacteria or anaerobes.**

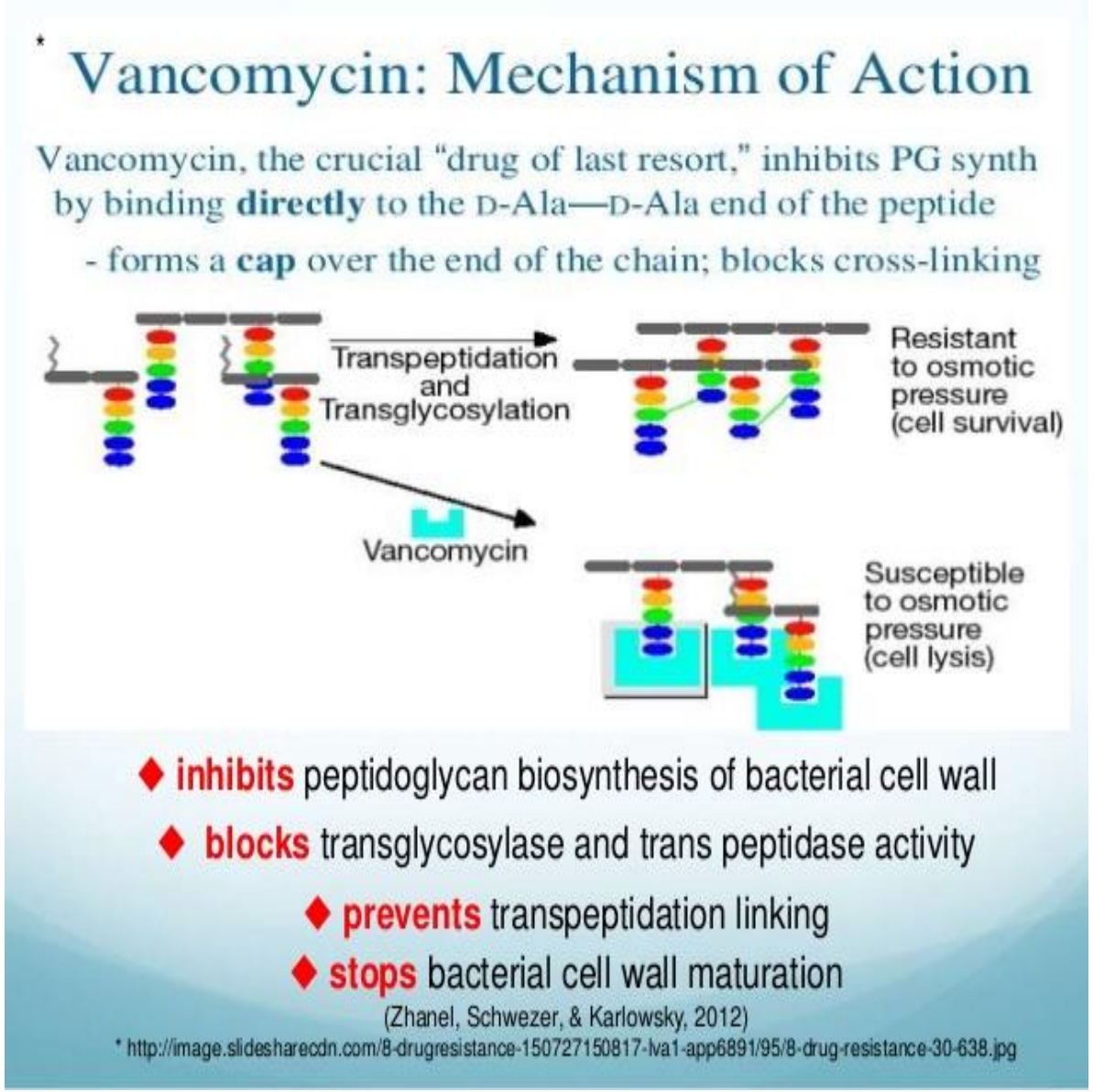
Vancomycin **is an antibiotic produced by Streptococcus orientalis and Amycolatopsis orientalis.**

It is active only against gram-positive bacteria.

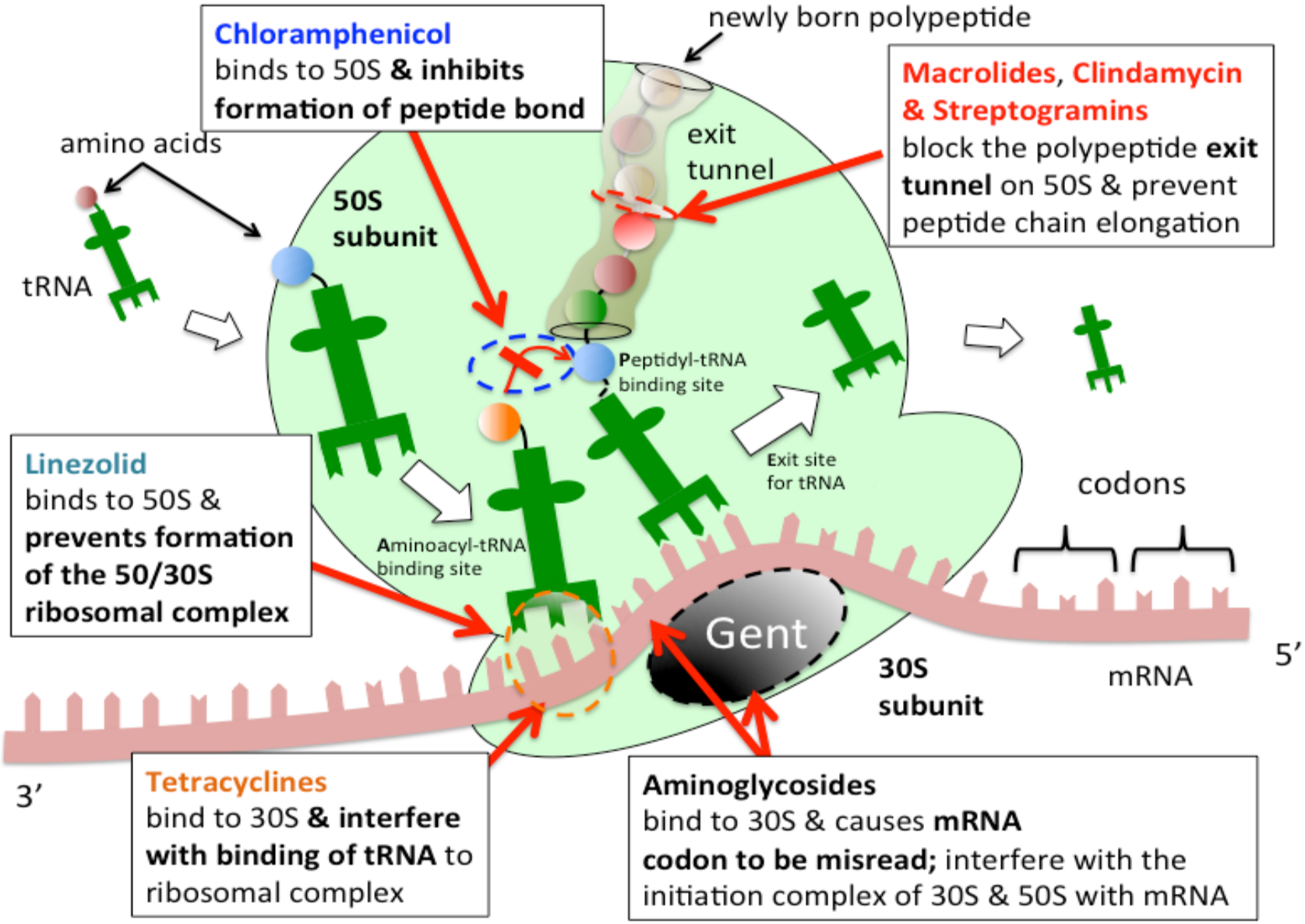
Vancomycin is a glycopeptide of molecular weight 1500. It is water soluble and quite stable.

USES:

- **Important indications for parenteral vancomycin are bloodstream infections and endocarditis caused by methicillinresistant staphylococci**
- **orally only for the treatment of colitis caused by C difficile**



Inhibition of bacterial protein synthesis



Thank You For Attention!

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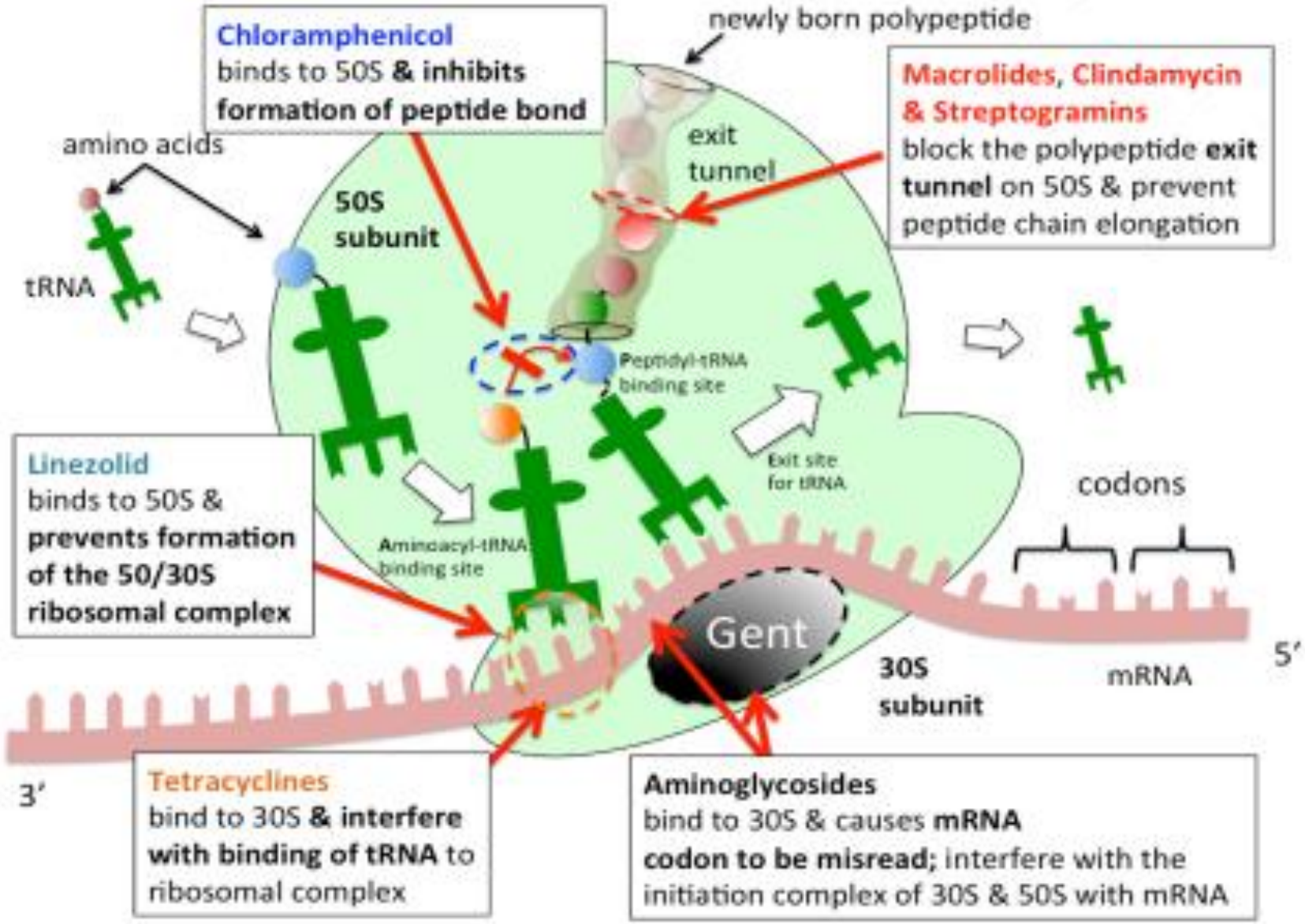
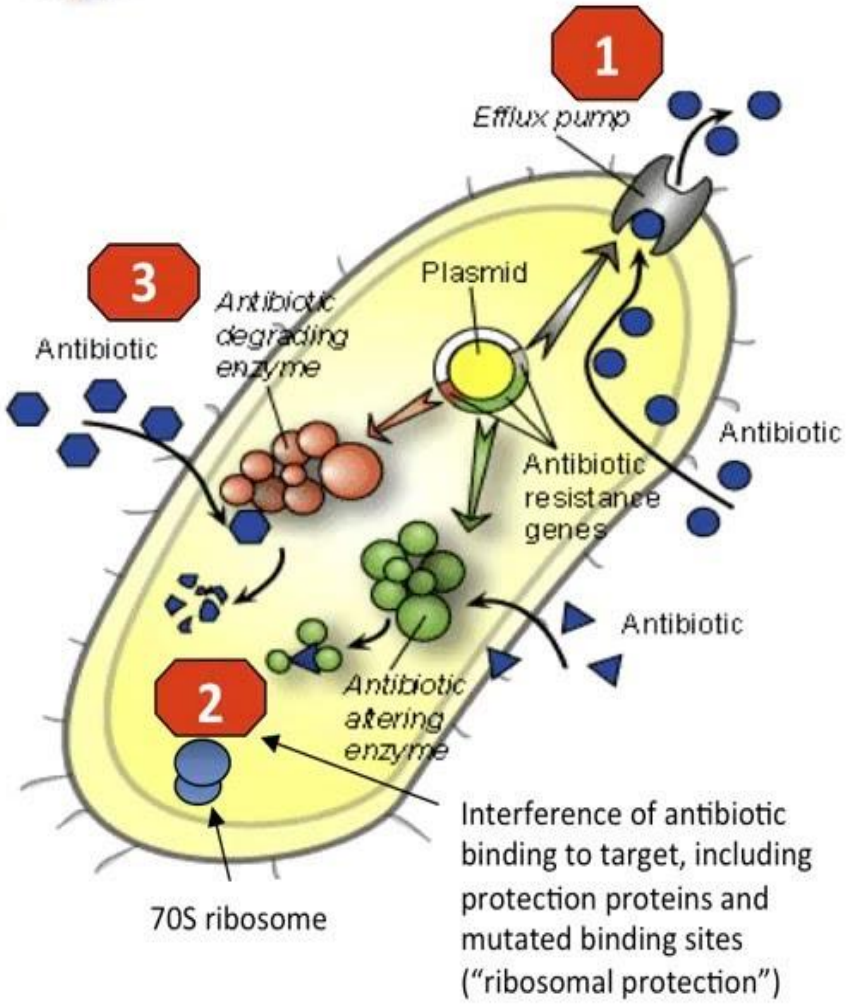
Inhibition of bacterial protein synthesis



Major Bacterial Resistance Mechanisms to Protein Synthesis Inhibitors



3 Major Mechanisms:

1. **Impaired influx or increased efflux**
   - E.g., Tet(AE) and Tet(K) efflux pumps (tetracyclines)
   - E.g., altered active transporters (aminoglycosides)
2. **"Ribosomal protection"**
   - E.g., Tet(M) ribosomal protection protein (tetracyclines)
   - E.g., "MLS_B resistance" vs. macrolides, lincosamides, and streptogramin B
3. **Enzymatic inactivation (degradation, alteration)**
   - E.g., bacterial esterases (macrolides)
   - E.g., acetyl-, phospho-, and adenylyltransferases (aminoglycosides)

Amphenicols : CHLORAMPHENICOL

Chloramphenicol has a wide spectrum of antimicrobial activity and is usually bacteriostatic (50S).

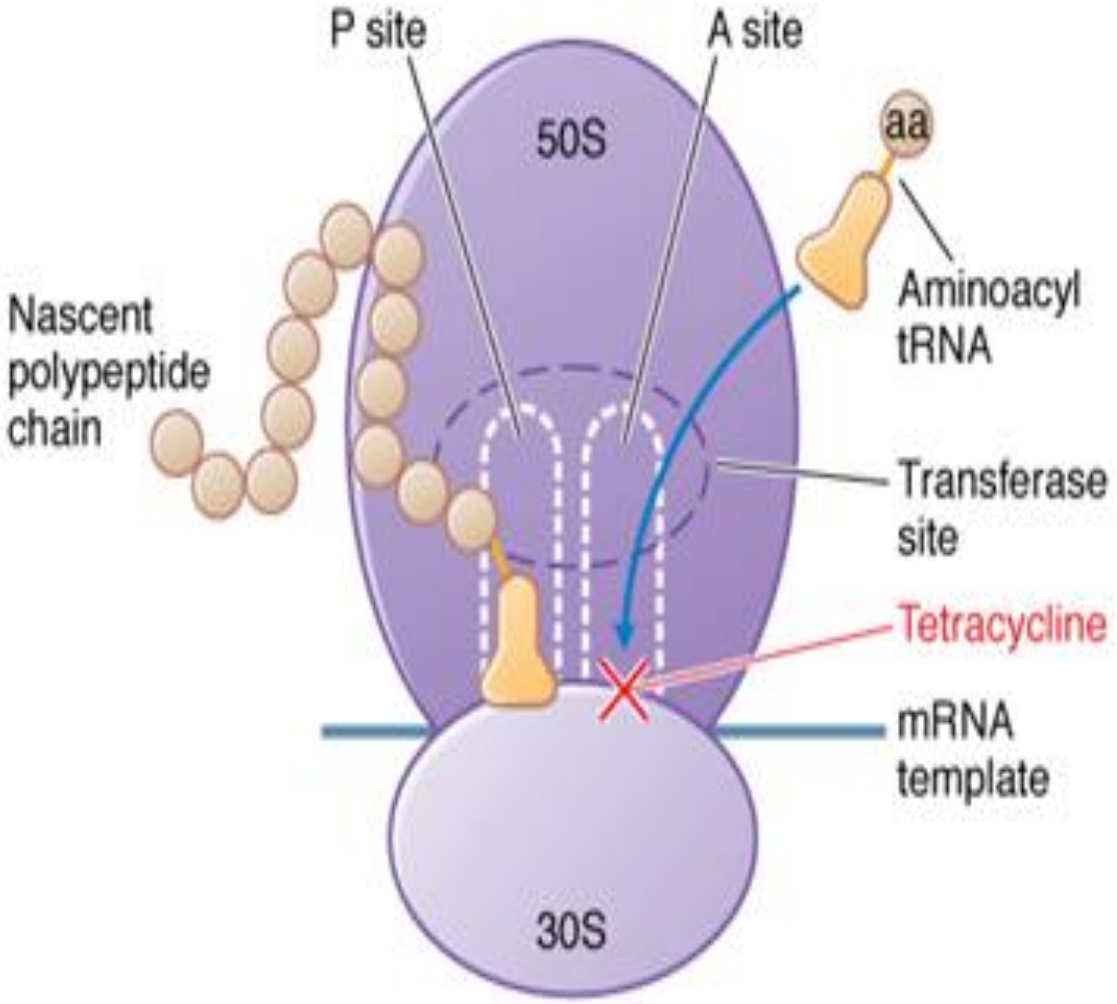
Clinical Uses

Because of its toxicity, chloramphenicol has very few uses as a systemic drug. It is a backup drug for severe infections caused by Salmonella species and for the treatment of pneumococcal and meningococcal meningitis in beta-lactam-sensitive persons.

Toxicity

1. **Gastrointestinal disturbances -** superinfection, especially candidiasis.
2. **Bone marrow -** Inhibition of red cell maturation leads to a decrease in circulating erythrocytes.
3. **Gray baby syndrome -** This syndrome occurs in infants characterized by decreased red blood cells, cyanosis, and cardiovascular collapse.
4. **Drug interactions -** Chloramphenicol inhibits hepatic drug metabolizing enzymes, thus increasing the elimination half-lives of drugs including phenytoin, tolbutamide and warfarin.

Tetracyclines



Mechanism of action

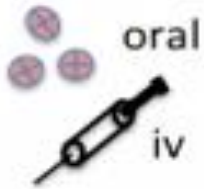
- **Tetracycline** inhibits protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome.
- **Tetracycline** binds to the 30S and 50S subunit of microbial ribosomes. Thus, it prevents introduction of new amino acids to the nascent peptide chain.

Tetracyclines -Toxicity

- Gastrointestinal disturbances
- Bony structures and teeth (tooth enamel dysplasia and irregularities in bone growth)
- Hepatic toxicity (impair liver function and lead to hepatic necrosis)
- Renal toxicity (renal tubular acidosis, Fanconi's syndrome)
- Photosensitivity (skin sensitivity to ultraviolet light)
- Vestibular toxicity

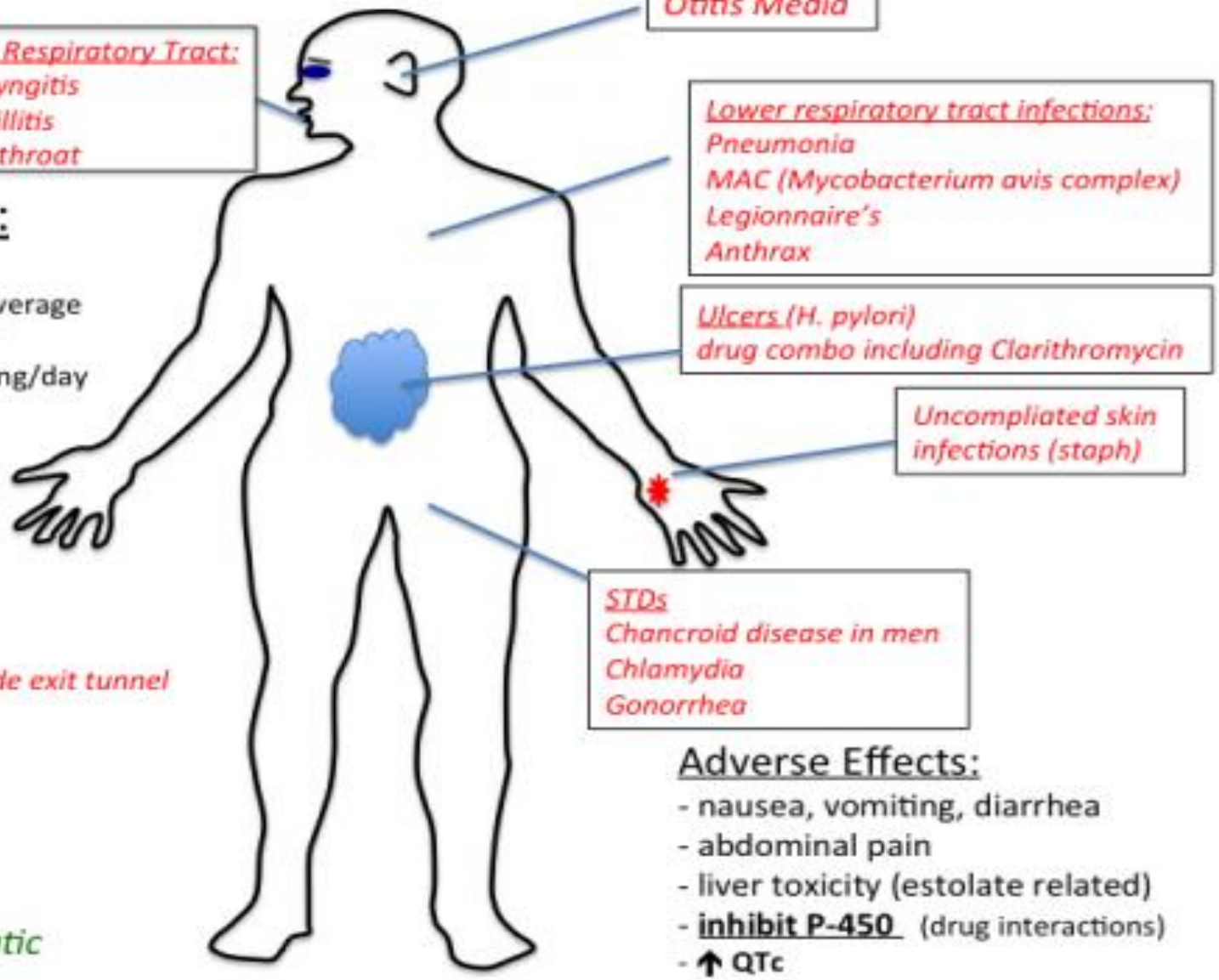
Macrolide Uses

Routes:



Pharmacokinetics:

- Azithromycin $t_{1/2}$ =3 days
- a 1 g dose provides 7 day coverage
- common therapy consists of 500 mg loading dose & 250 mg/day for 4 more days.



Upper Respiratory Tract:
- *Pharyngitis*
- *Tonsillitis*
- *Sore throat*

Otitis Media

Lower respiratory tract infections:
Pneumonia
MAC (Mycobacterium avis complex)
Legionnaire's
Anthrax

Ulcers (H. pylori)
drug combo including Clarithromycin

Uncompliated skin infections (staph)

STDs
Chancroid disease in men
Chlamydia
Gonorrhea

Mechanism:

Bind to 50S & block polypeptide exit tunnel to prevent chain elongation

bacteriostatic

Adverse Effects:

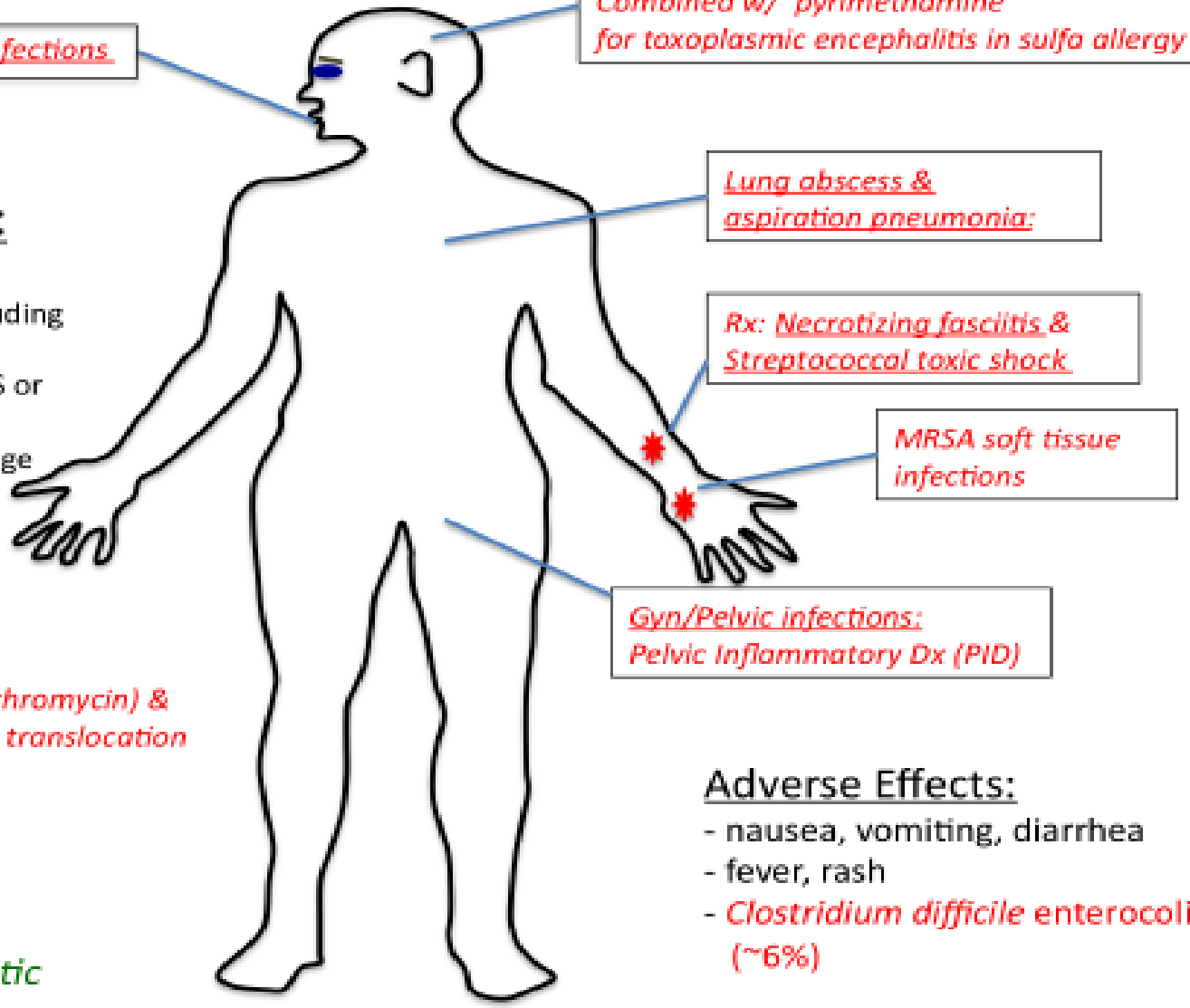
- nausea, vomiting, diarrhea
- abdominal pain
- liver toxicity (estolate related)
- **inhibit P-450** (drug interactions)
- ↑ QTc

Clindamycin Therapeutics

Routes:

Pharmacokinetics:

- $t_{1/2}$ = 2.5 hrs
- penetrates most tissues including abscesses
- does NOT penetrate into CNS or intracellular
- hepatic metabolism, no dosage adjustment with renal failure



Mechanism:

Binds to 50S (same site as erythromycin) & inhibits peptidyl transferase & translocation

bacteriostatic

Adverse Effects:

- nausea, vomiting, diarrhea
- fever, rash
- *Clostridium difficile* enterocolitis (~6%)

Aminoglycoside Uses

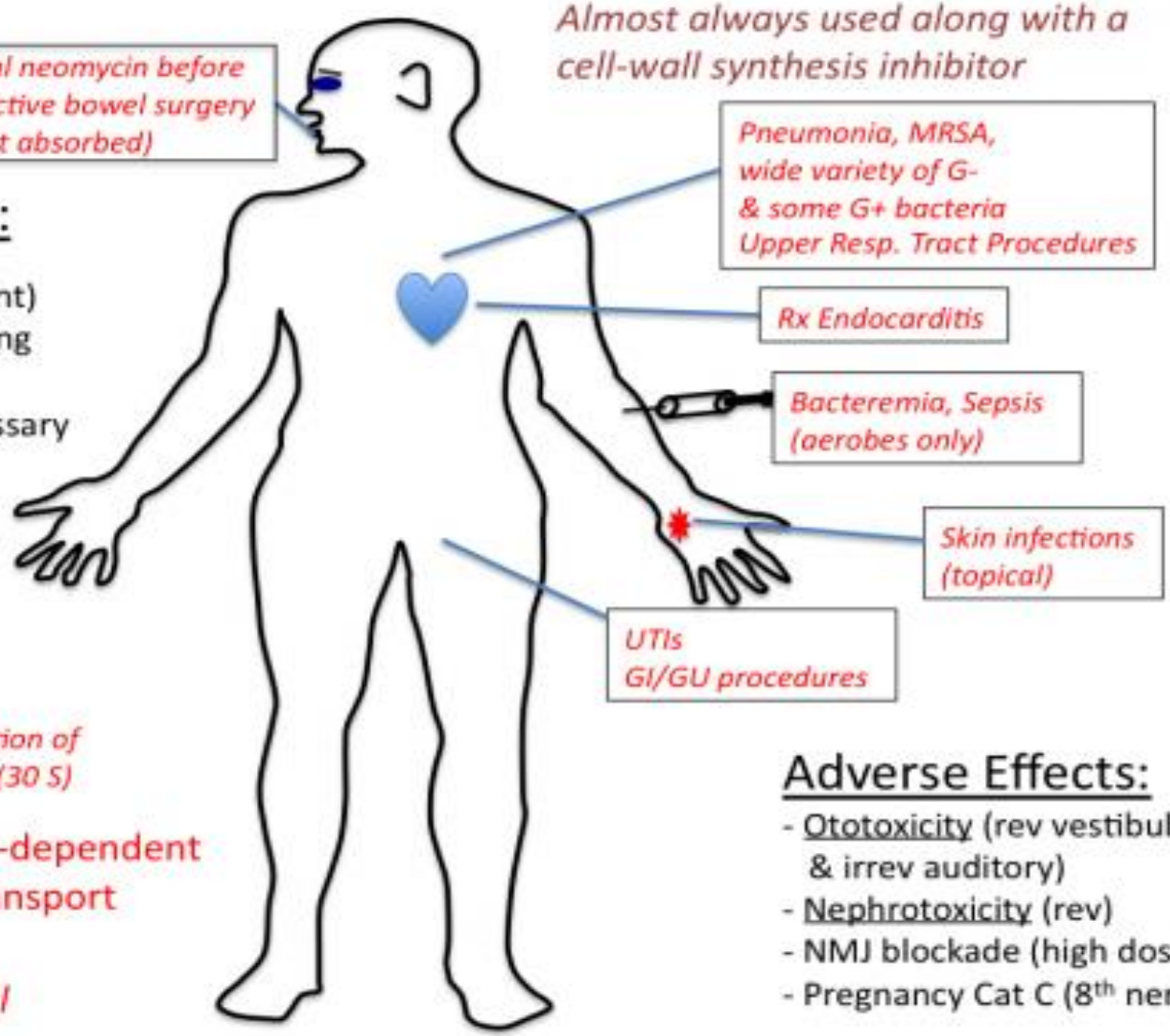
Routes:

im *or* iv,
topical

Pharmacokinetics:

-Vd = ECS (25% body weight)
- adjust maintenance dosing based upon [creatinine]
- plasma monitoring necessary

Almost always used along with a cell-wall synthesis inhibitor



Oral neomycin before elective bowel surgery (not absorbed)

Pneumonia, MRSA, wide variety of G- & some G+ bacteria Upper Resp. Tract Procedures

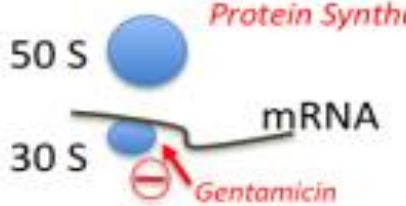
Rx Endocarditis

Bacteremia, Sepsis (aerobes only)

Skin infections (topical)

UTIs GI/GU procedures

Mechanism:



Irreversible inhibition of Protein Synthesis (30 S)

O_2-dependent transport

bactericidal

Adverse Effects:

- Ototoxicity (rev vestibular & irrev auditory)
- Nephrotoxicity (rev)
- NMJ blockade (high dose)
- Pregnancy Cat C (8th nerve)

Thank You For Attention!

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