

Antimicrobial therapy

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Main Contents:

1. Introduction and history
2. Different classes of antibiotics and its Mechanism of action
3. Basic principles on usage
4. Resistance

Antibacterial therapy

- Antimicrobial chemotherapy
- What is an Antibiotics?

- Egyptians 1500BC: Honey for wounds
- Alexander Fleming and Louis Pasteur

Antibacterial therapy

- 2000 B.C. - "Here, eat this root."
- 1000 B.C. - "That root is heathen, say this prayer."
- 1850 A.D. - "That prayer is superstition, drink this potion."
- 1940 A.D. - "That potion is snake oil, swallow this pill."
- 2000 A.D. - " That pill or antibiotic is ineffective. Here, eat this root."
~Author Unknown

The Bright side

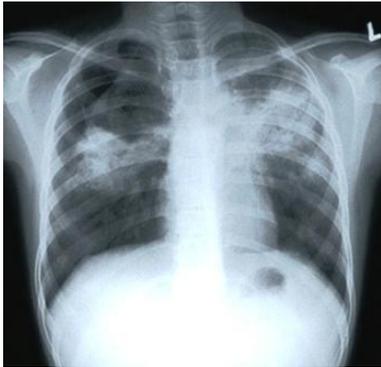
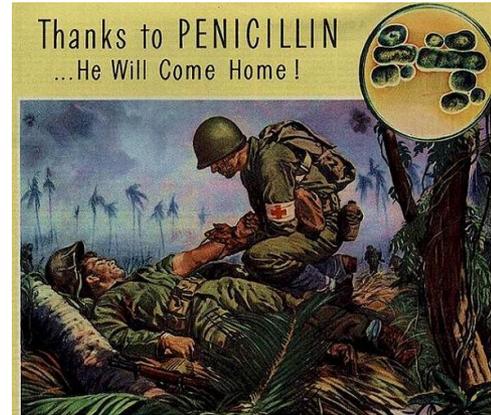
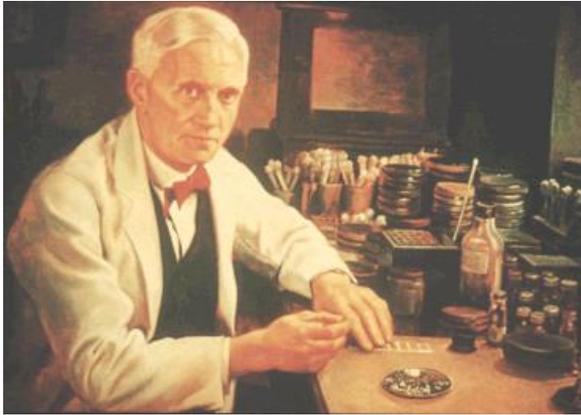
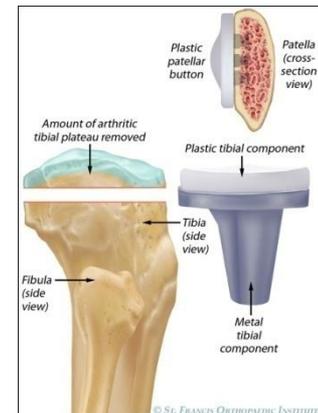


Figure 1 - Necrotizing fasciitis covering the anterior face of the left leg: generalized edema, violet-colored skin, blisters, and bloody regions.

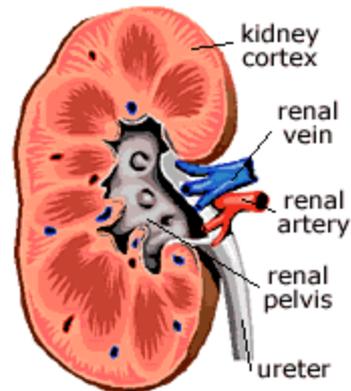
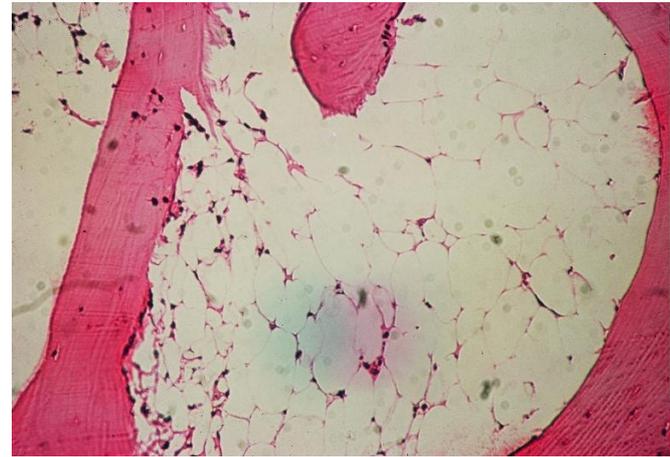


Yet even life savers may



- take life
- (remember!
Antibiotics are
**DANGEROUS
DRUGS!!**)

Because antibiotics are DANGEROUS DRUGS



C deathicille (difficile)

- A UK Consultant Microbiologists nightmare !



Antibacterial therapy

> Antibiotics: natural products derived from soil bacteria and fungi

Examples:

Penicillin from penicillin notatum mould (Alexander Fleming)

> Semisynthetic agents:

Natural compounds that have been chemically modified to increase its activity and improve pharmacokinetics

Examples:

Cephalosporins and Carbapenems.

Antibacterial therapy

Synthetic chemicals:

Trimethoprim and linezolid, quinolones are examples

Antibiotics are loosely applied to all antibacterial agent

- Terms related to antibiotics use:
- Synergism
- Broad vs narrow spectrum
- Empirical use?
- Selective toxicity
- Static vs cidal (MIC vs MLC)

Antibacterial therapy

Basic principles:

- Selective toxicity:

Kill or inhibit the growth of microorganism without harming human tissue.

- Bactericidal versus bacteriostatic **FIGURE 1**

Bactericidal: minimum lethal concentration (MLC)

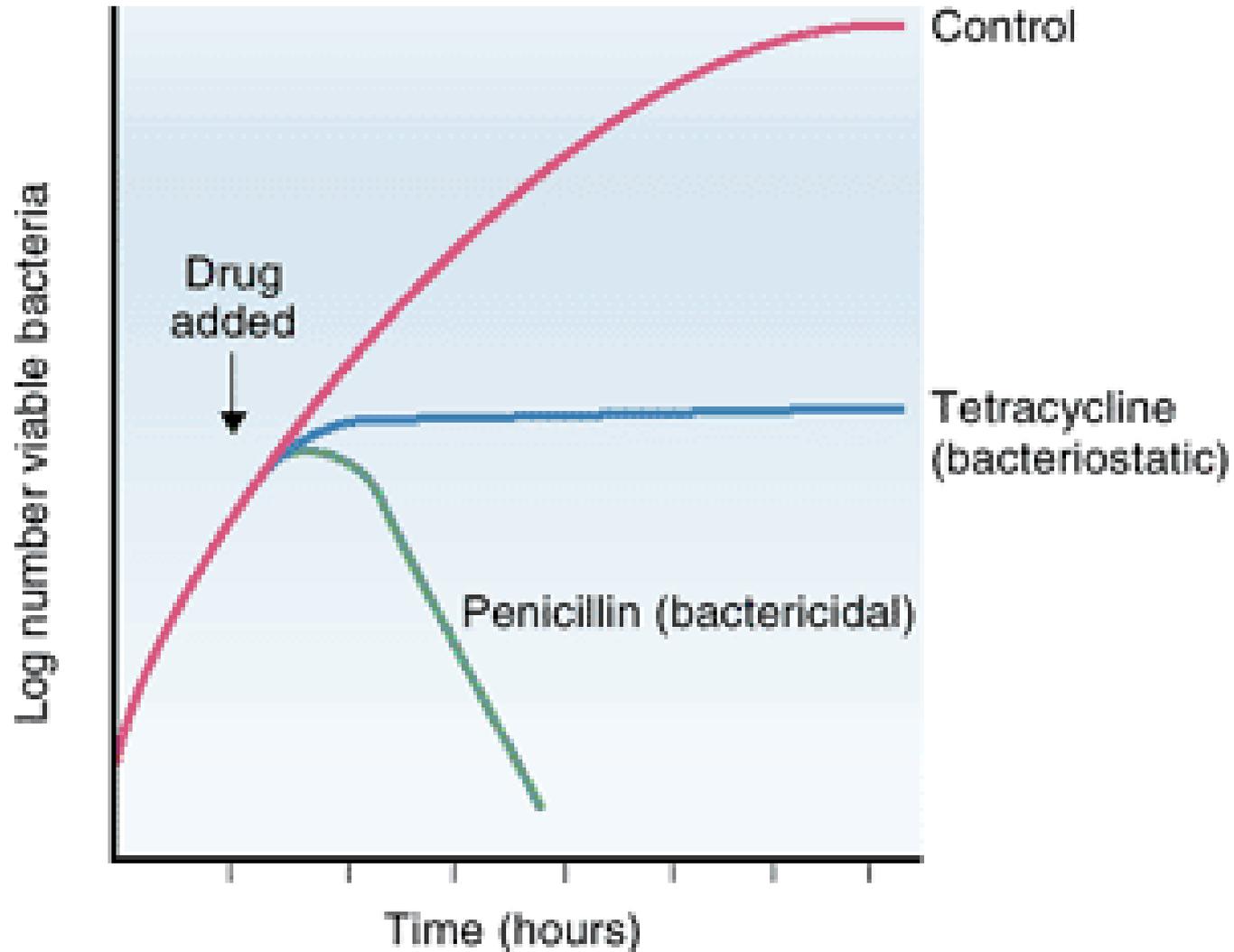
Bacteriostatic: minimum inhibitory concentration(MIC)

- Some infections such as infective endocarditis or immunocompromised patients > Bactericidal is a must

Antibacterial therapy

- Bacteriostatic allows for natural immunity to deal with the microbe
 - Antibodies, Phagocytosis etc
- Bactericidal may rarely lead to release of toxins and microbial contents leading to subsequent illness and inflammatory responses.

Antibacterial therapy Figure 1



Antibacterial therapy/

Indications for use / to avoid abuse:

1. Treat infections empirically / culture sensitivity.
2. Prophylaxis/ limited situations.

Abuse:

Side effects

Resistance

Cost-effectiveness

Antibacterial therapy/

Route of administration:

- Nature of infection
- Bioavailability and therapeutic index or window
- Tissue penetration, excretion, pharmacokinetics

Precautions:

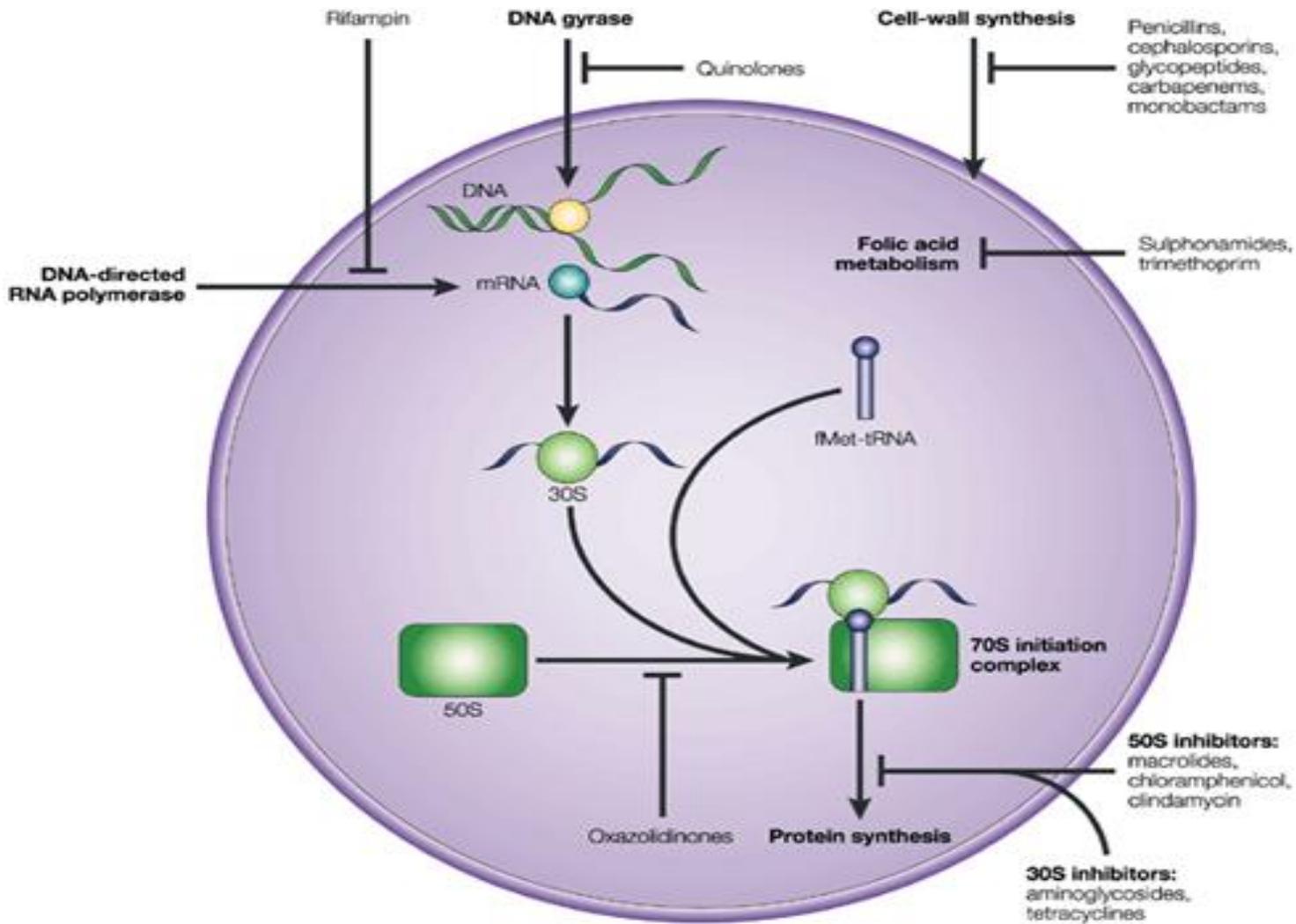
- >History of hypersensitivity
- >Impaired liver and kidney functions
- >Pregnancy, breastfeeding and children

Antibacterial therapy

Target of antibacterial agents: Figure 2:

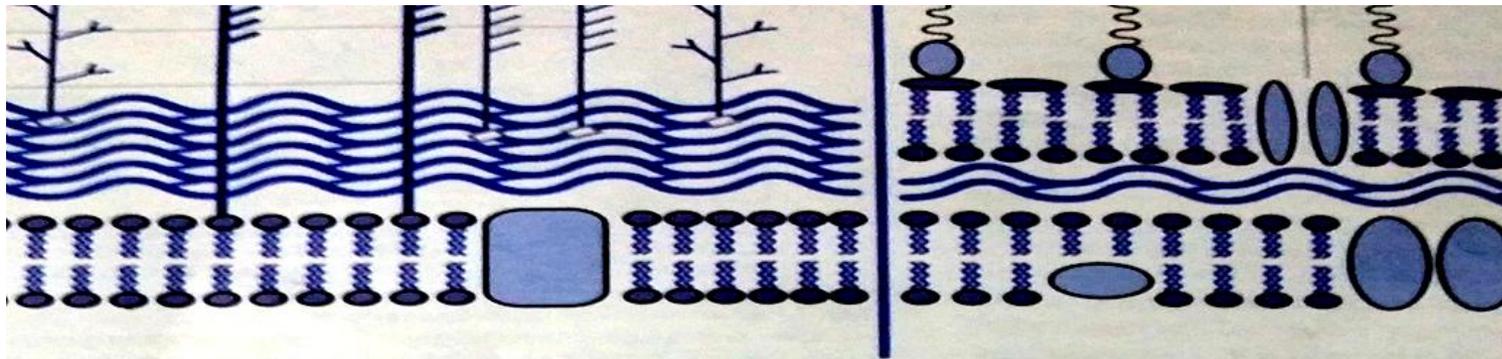
- Cell wall: Peptidoglycan?
- Protein synthesis: Ribosome 70S versus 80S
- Folate synthesis:
Bacteria manufacture its own folates while human obtain it in food
- Nucleic acid synthesis
- Other sites such as bacterial cell membrane

Antibacterial therapy Figure 2/ Antibiotics target

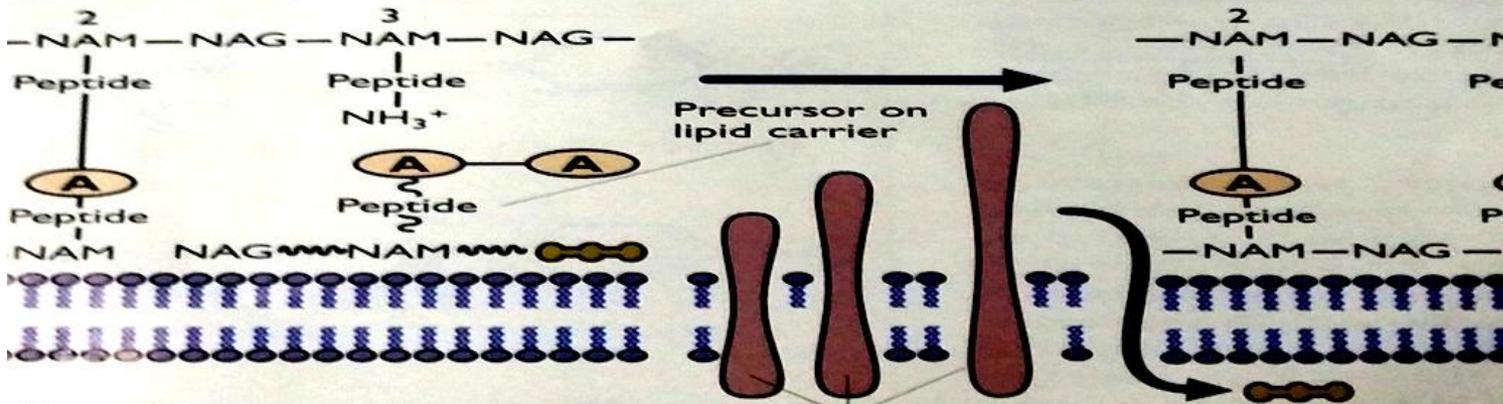


1- Antibacterial therapy/Inhibition of cell wall synthesis

- Most bacteria possess a cell wall to protect from osmotic pressures
- Microbe divides – needs to create a new cell wall
 - Interrupt this leads to new microbes being susceptible to external influences
 - Cell ruptures → Microbe death
- Eg. Penicillins cephalosporins, vancomycin and bacitracin
- Spectrum of activity:



cell wall of gram-positive and gram-negative bacteria.



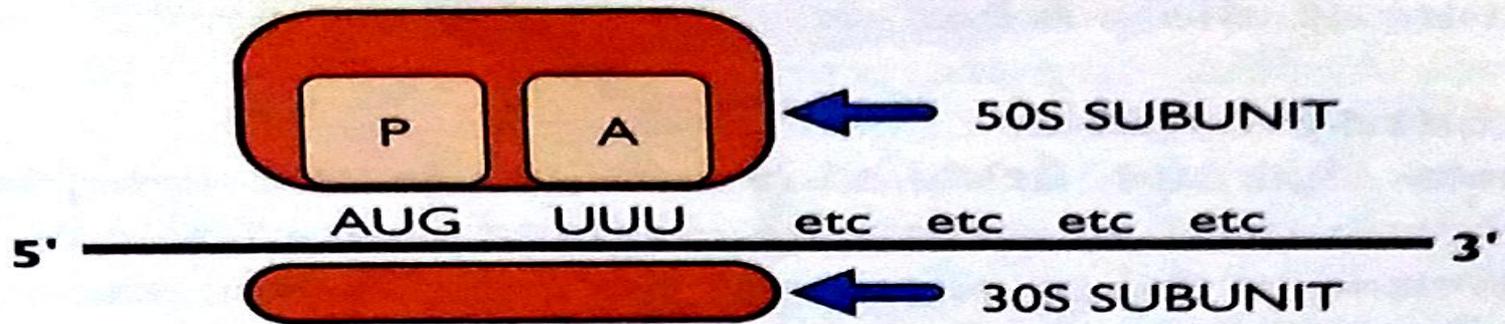
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rier

Penicillin binding proteins =
trans- and carboxypeptidases

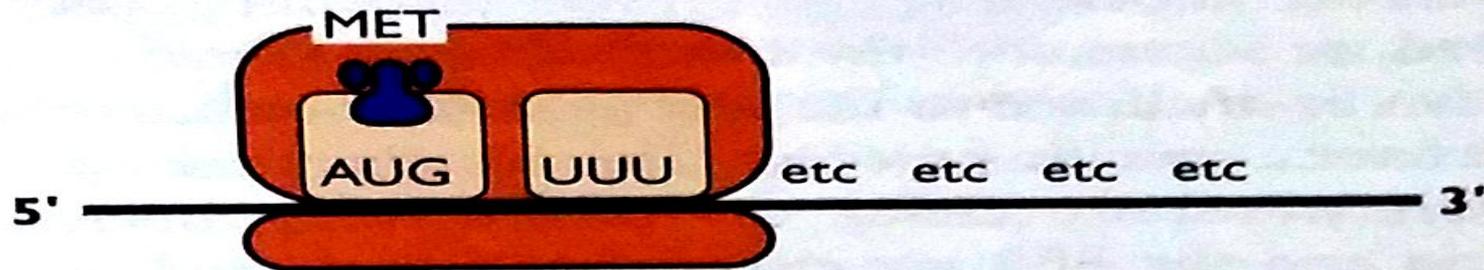
of repeating units of N-acetylglucosamine (NAG) and N-acetylmuramic acid
proteins (PBP) are responsible for cross-linking these peptide side chains.

2. Antibacterial therapy / inhibition of microbial protein synthesis

- Act at site of protein synthesis (ribosome)
- Tetracyclines (static), chloramphenicol (static) aminoglycosides (cidal) and macrolides (static), e.g erythromycin, clindamycin (static).



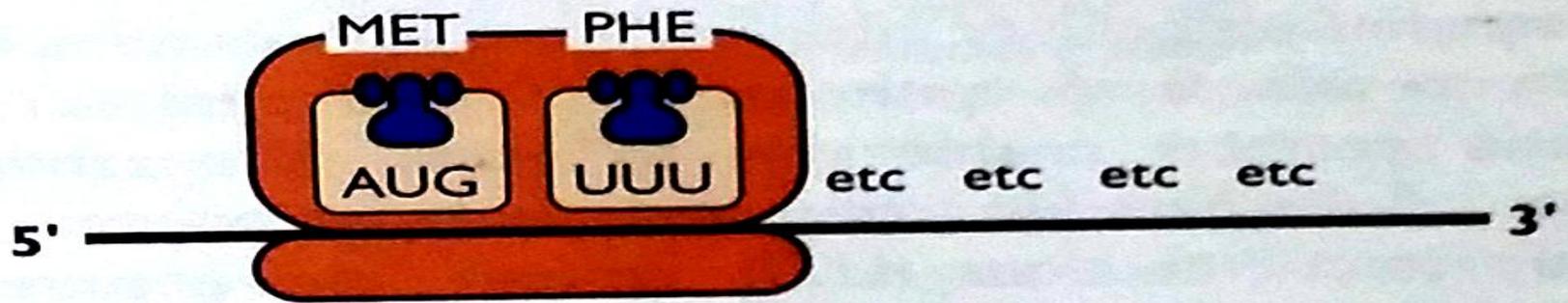
Initiation complex formed



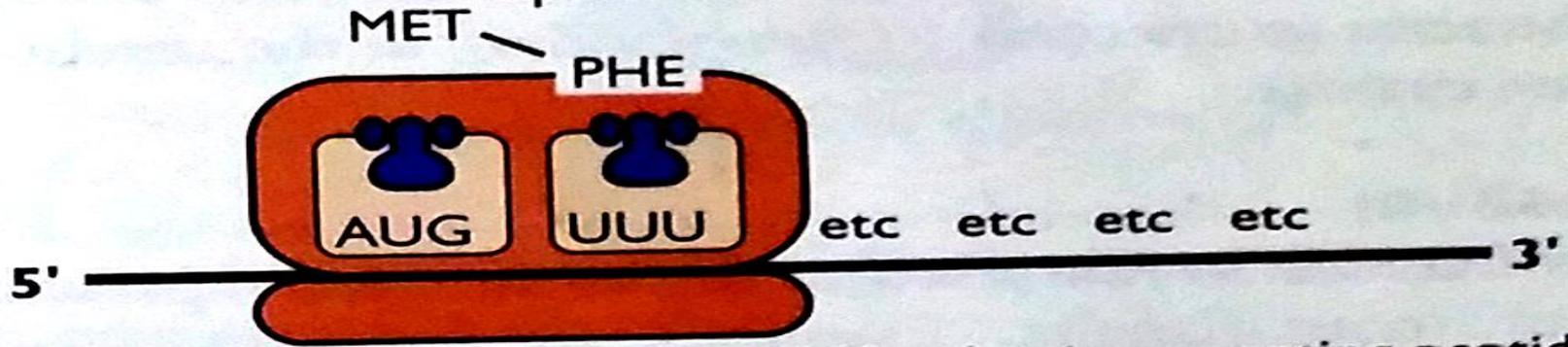
Aminoglycosides (e.g. gentamicin) bind to the 30S subunit and prevent peptide chain initiation

Spectrum of activity:

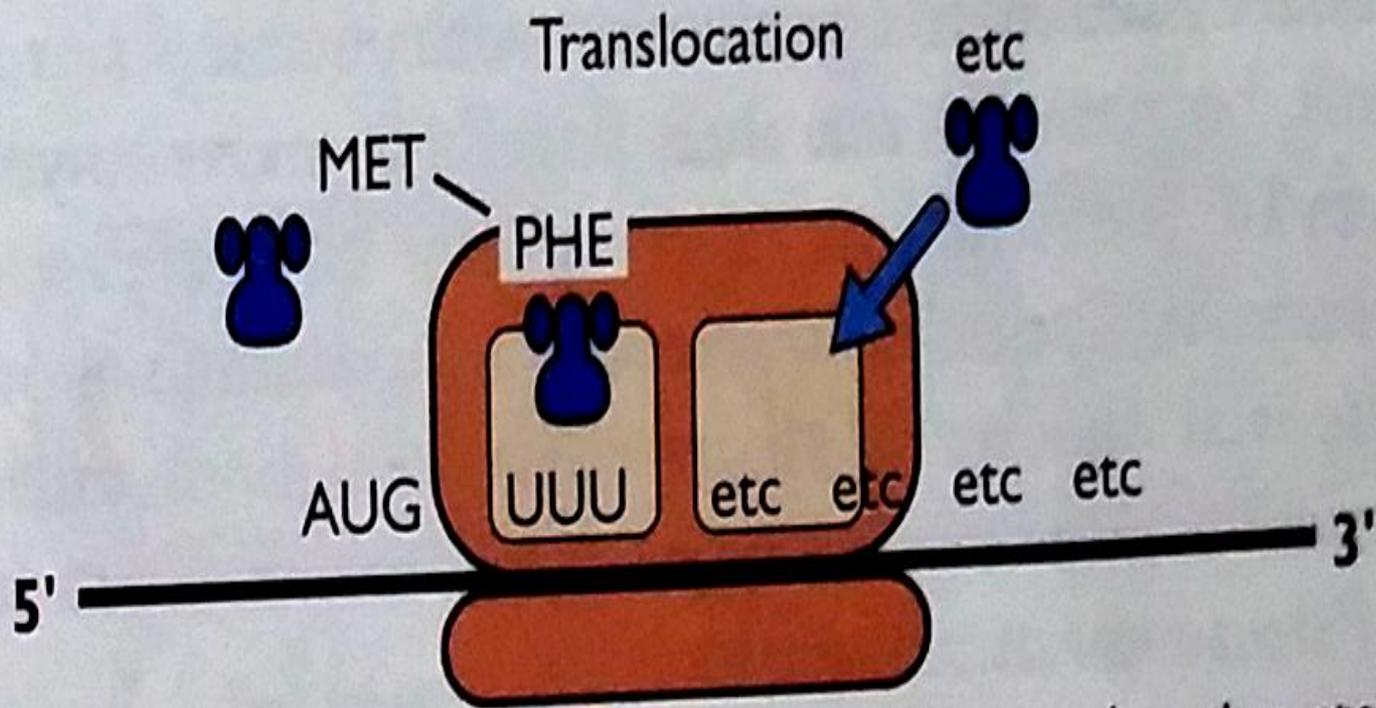
Second amino acid enters A site



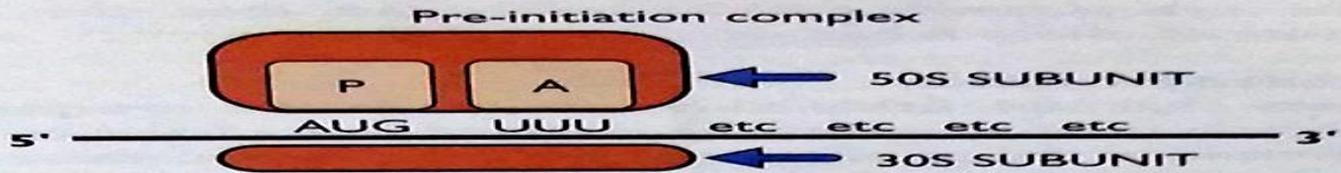
Peptide bond formation



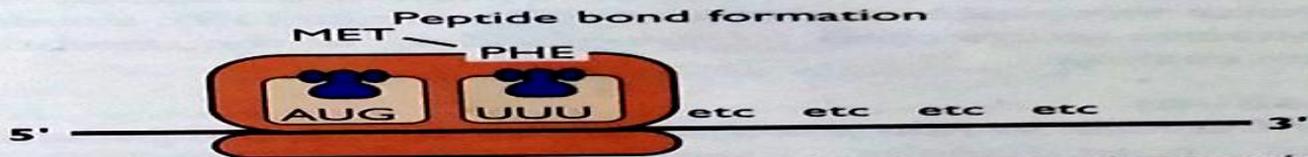
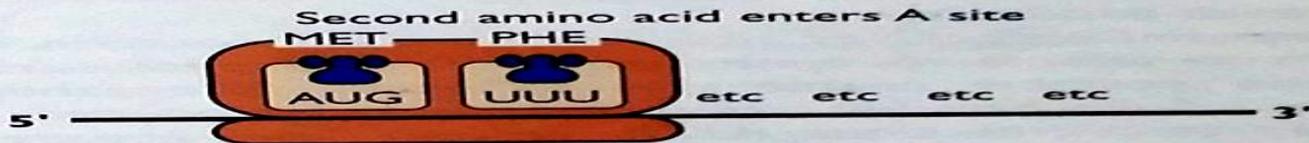
Chloramphenicol binds to the 50S subunit preventing peptide bond formation



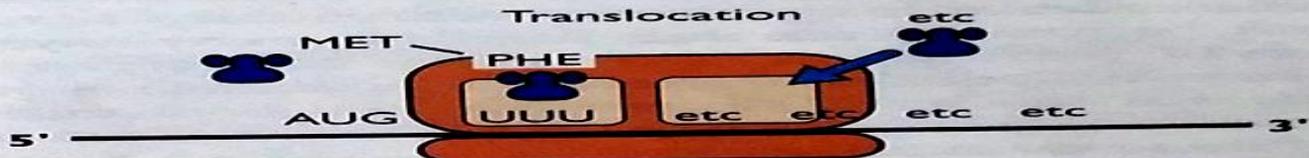
The macrolide erythromycin can prevent the translocation step by interfering with release of the 'free' tRNA from the P site



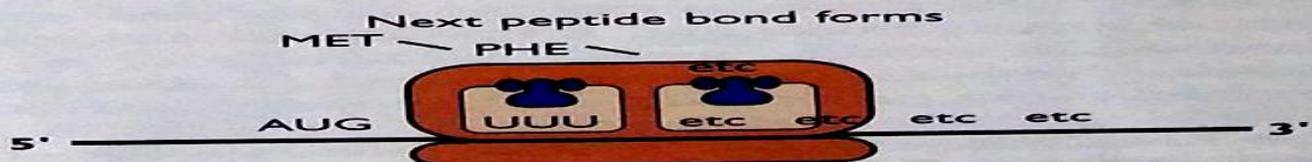
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Chloramphenicol binds to the 50S subunit preventing peptide bond formation



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3. Antibacterial therapy/Inhibition of folates synthesis

- Eg Sulphonamides, Trimethoprim (static)
- Available as combination, Co-trimoxazole, or separately

p-aminobenzoic acid + Pteridine

Sulfonamides

**Pteridine
synthetase**

Dihydropteroic acid

**Dihydrofolate
synthetase**

Dihydrofolic acid

Trimethoprim

**Dihydrofolate
reductase**

Tetrahydrofolic acid

Thymidine

Purines

Methionine

4. Antibacterial therapy/Inhibition of nucleic acid synthesis and function

- **A. INHIBITORS OF RNA SYNTHESIS AND FUNCTION**

 - **Rifampicin (bactericidal)**

 - a. Mode of action

These antimicrobials bind to DNA-dependent RNA polymerase and inhibit initiation of mRNA synthesis

 - b. Spectrum of activity

They are wide spectrum antibiotics but are used most commonly in the treatment of tuberculosis and MRSA

 - c. Combination therapy

Since resistance is common, rifampin is usually used in combination therapy

Antibacterial therapy/Inhibition of nucleic acid synthesis and function

- **b. Inhibitors of DNA synthesis and function**

Quinolones - nalidixic acid, ciprofloxacin, oxolinic acid (bactericidal)

- Mode of action

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

Antibacterial therapy

Resistance: meaning?

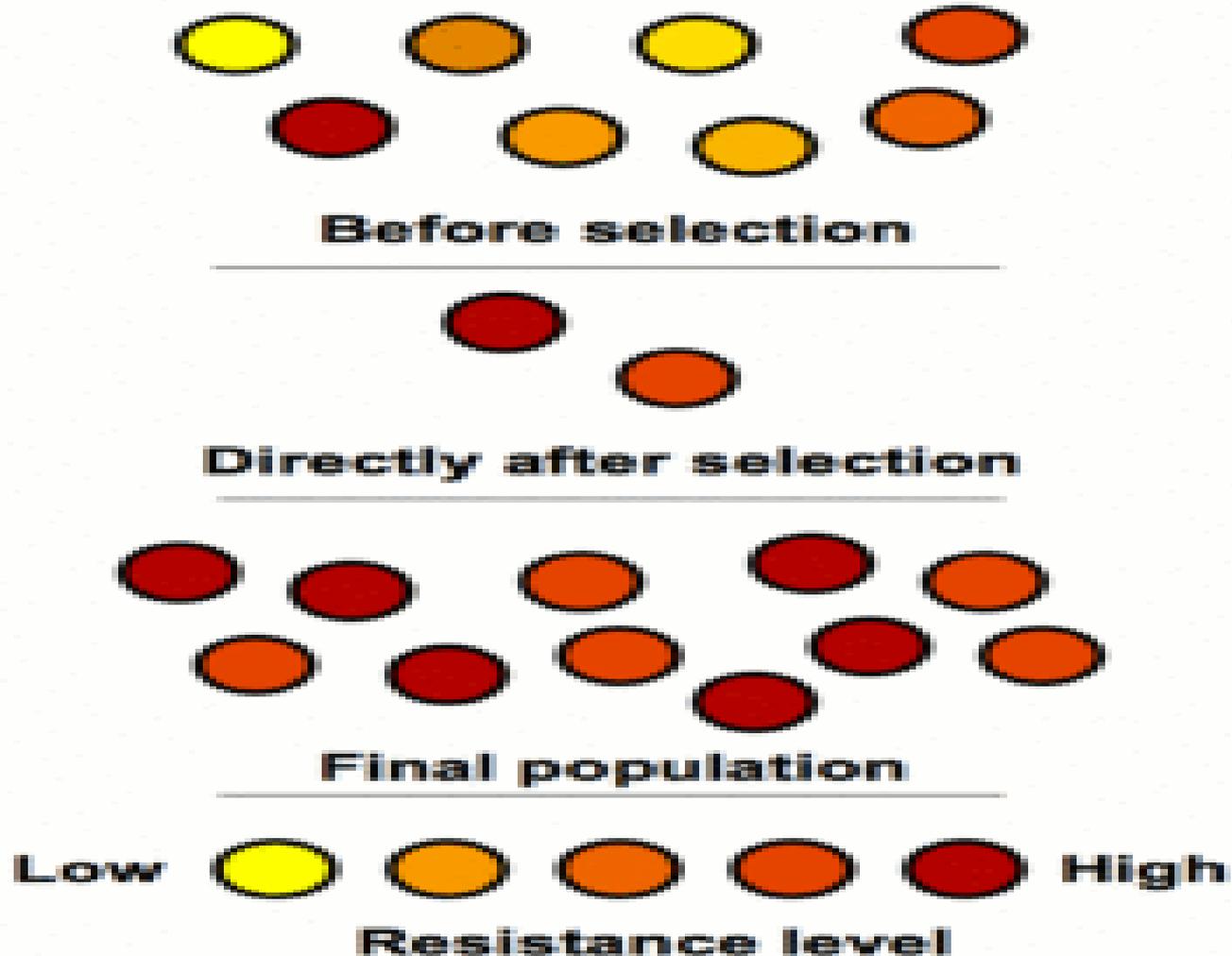
Types and terms:

Intrinsic or inherent: no target site or cell wall is impermeable to antibiotics as in gram negative bacteria (vancomycin is too big to cross the cell wall)

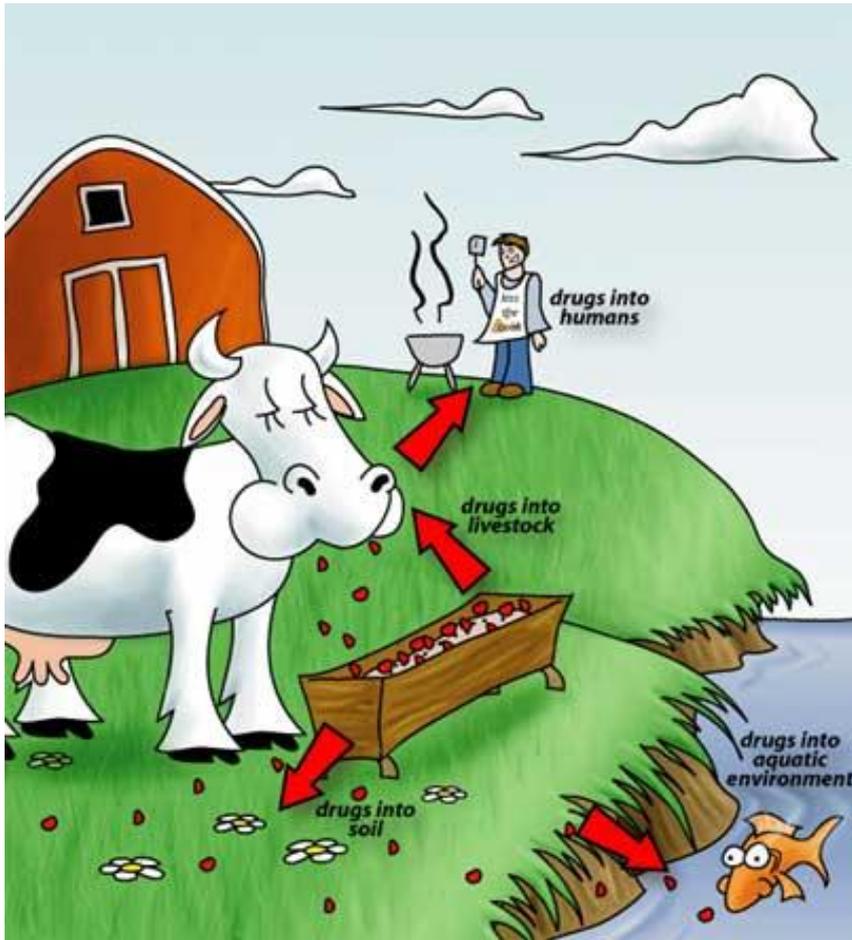
Acquired resistance:

- Selection of resistant bacteria by antibiotics
- Common in areas of heavy antibiotic misuse e.g hospitals
- The resistance is initially emerged by genetic process then selected by antibiotics **FIGURE 3**

Antibacterial therapy / Figure 3



Extra wrinkle here



- Doctors/nurse prescribers are not the only culprits!!!
- > examples of R bugs due to agricultural overuse/misuse??
- NB the food chain!!

Antibacterial therapy

Cross resistance:

Resistance to one member of a family will result in resistance or decreased susceptibility to other members within the same family e,.g
fluroquinolones

Multiresistance:

Resistance to more than one antibacterial
Usually acquired by separate mechanisms

Genetics of resistance:

Chromosomal mutations

Genetic transfer

Antibacterial therapy

Mechanism or resistance: FIGURE 4

1. Decreased accumulation:

Decreased permeability secondary to porins mutations

Increased efflux (pumping out the antibacterial using expressed efflux pump)

Antibacterial therapy

2. Modification of the target:

- Sequence mutation leading to target alteration
e.g in pneumococcus resistance to penicillins >

- Target bypass:

Supplementary enzymes will do the same target function but without binding to the antibacterial agent e.g Meticillin resistant staph aureus MRSA (PBP2 coded by mec A gene)

- Target hyperproduction:

More drug is needed to inactivate the target

Antibacterial therapy

3. Inactivation of the antibacterial agent:

- β lactamase is an enzyme produced by the bacteria

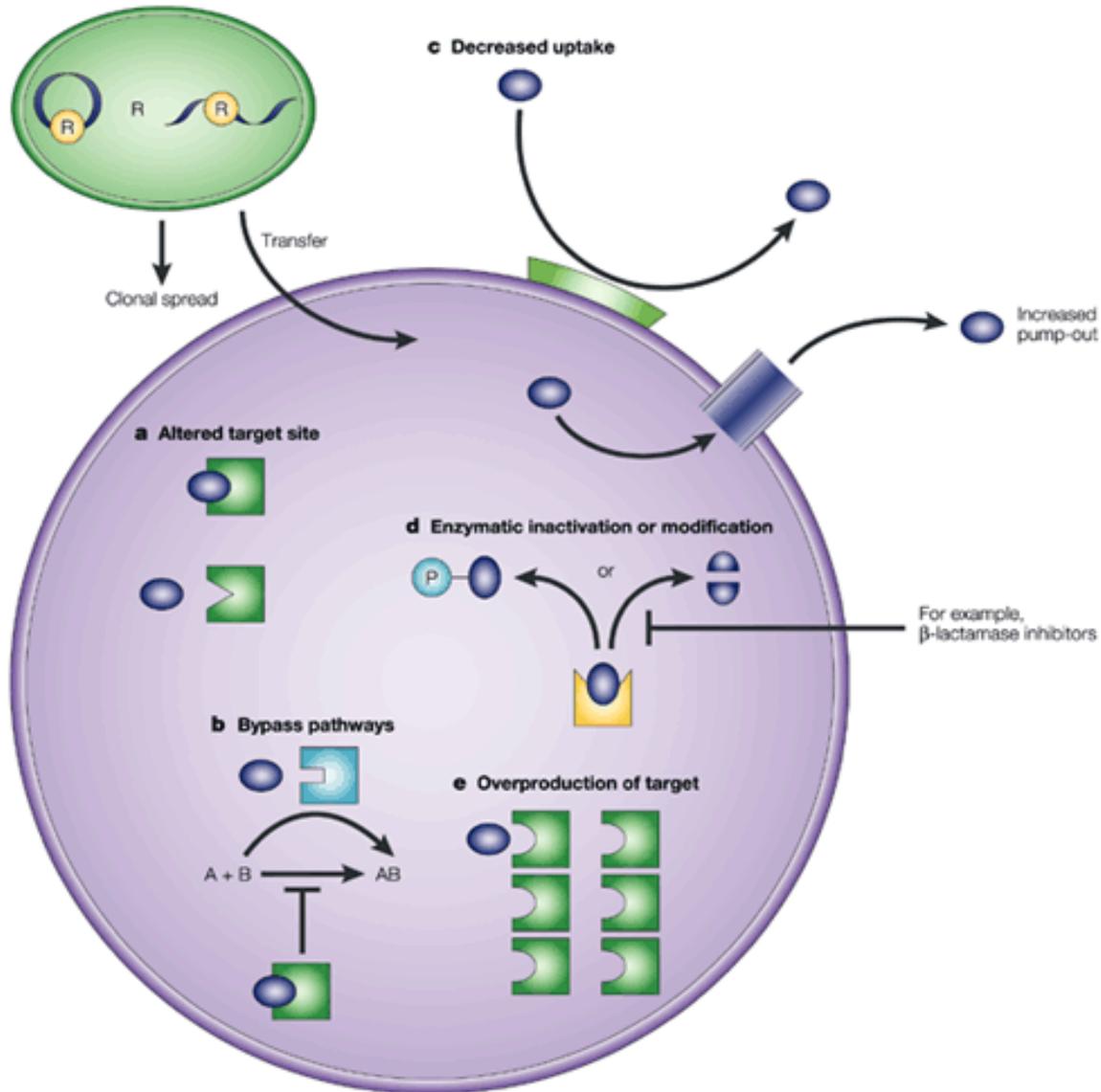
This enzyme will destroy the β - lactam ring (this is an essential ring in penicillins and cephalosporins) leading to inactivation of the antibacterial agent

- Some types of bacteria produce a β - lactamase with a wide range of activity (ESBLs)

Acetylating, adenylating and phosphorylating enzymes:

Produced by bacteria (gram negative bacteria) and cause resistance to aminoglycosides and chloramphenicol

Antibacterial therapy / Figure 4



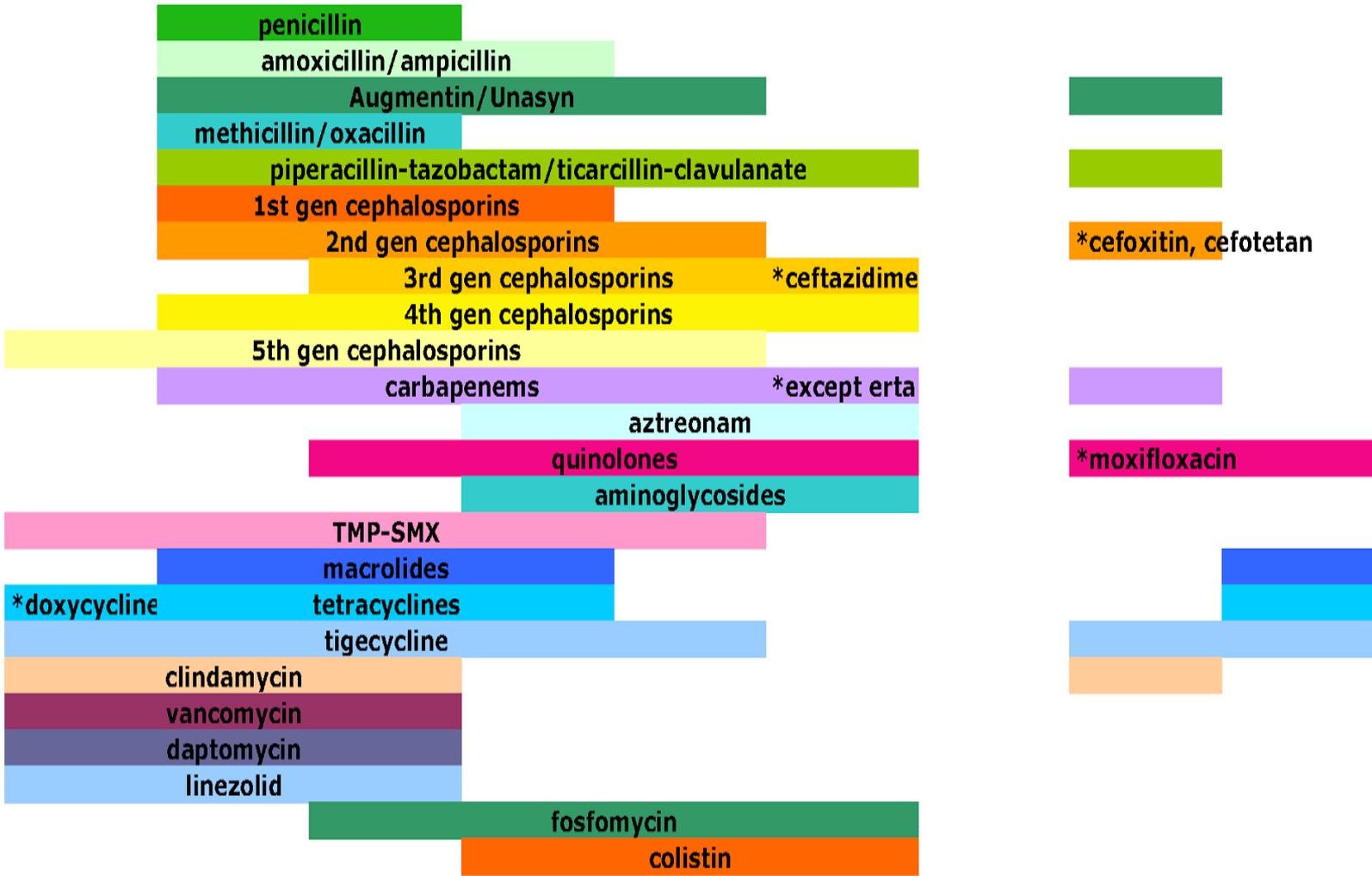
MRSA

GRAM POSITIVES

GRAM NEGATIVES

Pseudomonas

ANAEROBES ATYPICALS



The End