Antibiotics

Learning objectives

- Definitions
- Targets for antibiotic action
- Normal peptidoglycan & Protein synthesis in bacteria
- Mechanism of Action of Important Antibacterial and Antifungal Drugs

- **Antibiotic-** Chemical agents produced by micro-organisms that kill or inhibit other micro-organisms.
- **Antimicrobial agents-** agents of synthetic origin useful in the treatment of microbial or viral disease.
- **Probiotics-** Live, nonpathogenic bacteria, which excludes the pathogen from binding sites on the mucosa (colonization resistance)

- **selective toxicity**; selective inhibition of the growth of the microorganism without damage to the host.

Basis is non-similarity of structure & function

Actions

- Bactericidal = kill bacteria
- Bacteriostatic = slow or interfere with growth of bacteria

- **Broad-spectrum** antibiotics active against several types of microorganisms, e.g., tetracyclines are active against many gram -negative rods, chlamydiae, mycoplasmas, and rickettsiae.
- **Narrow-spectrum** antibiotics active against one or very few types, e.g., vancomycin is primarily used against certain gram -positive cocci namely , staphylococci & enterococci

Definition

- *Ideally, culture of suspect area should be done BEFORE starting antibiotic*

Uses

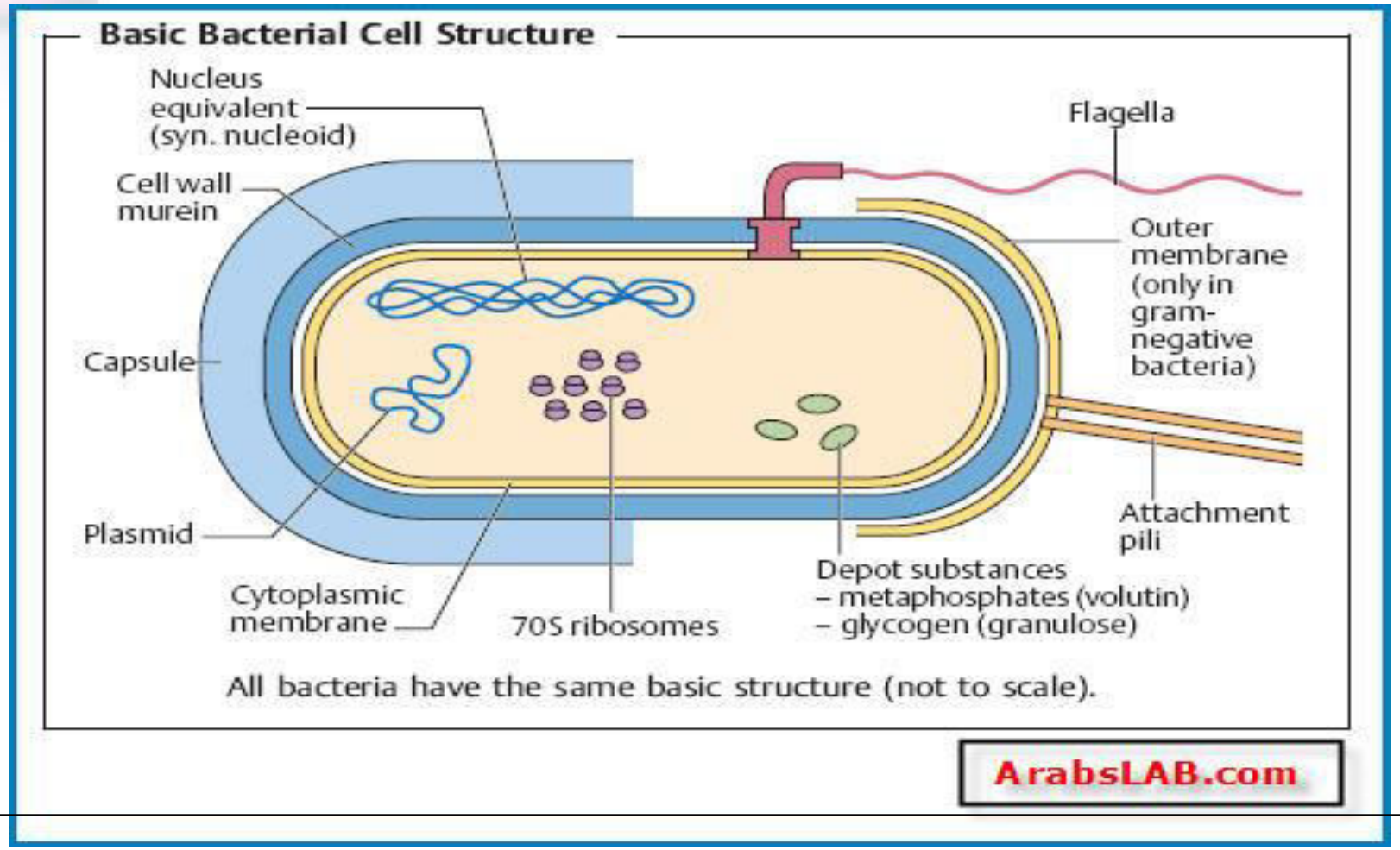
- Treatment of existing infection
- Prevention of infection- Chemoprophylaxis in three circumstances:

a. prior to surgery
b. in immunocompromised patients
c. In people with normal immunity who have been exposed to certain pathogens.

- In patients undergoing dental, GI tract, or GU tract surgery who have a damaged heart valve or a prosthetic heart valve.
- Patients undergoing dental surgery are at risk for endocarditis caused by viridans streptococci should be given amoxicillin perioperatively . Patients undergoing GI tract or GU tract surgery are at risk for endocarditis caused by enterococci and should be given ampicillin and gentamicin perioperatively .
- in patients with prosthetic joints or vascular grafts undergoing dental, GI tract or GU tract surgery
- Prevention of infection of prosthetic joints or vascular grafts

- But there are far more antibacterial drugs than antiviral drugs.
- WHY
- Because viruses use host cell in their growth

Targets for antibiotic action



4 majorTargets for antibiotic action

- cell wall
- cell membrane
- protein synthesis
- nucleic acid

Mechanism of Action of Important Antibacterial and Antifungal Drugs

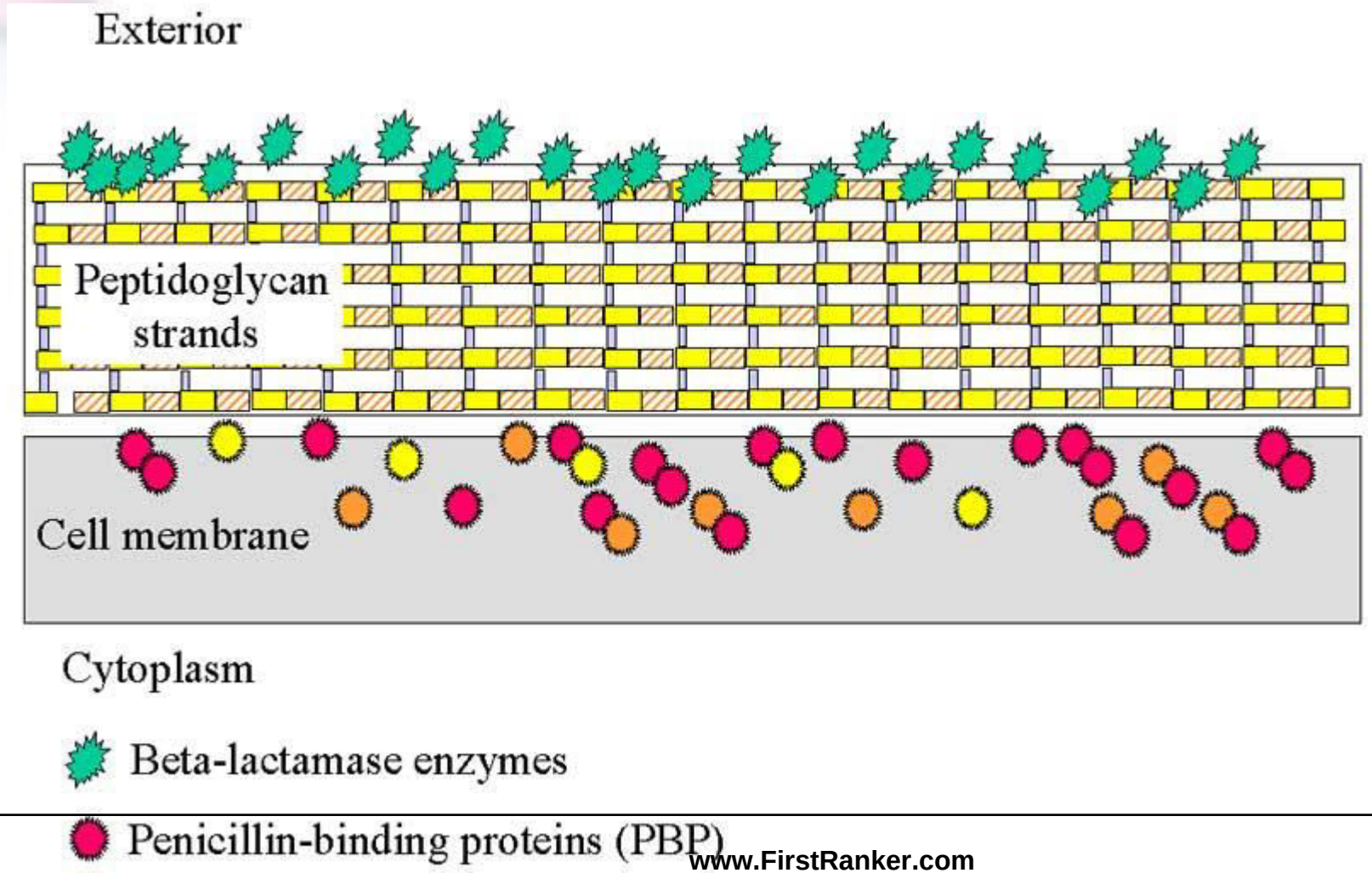
Mechanism of Action	Drugs
Inhibition of cell wall synthesis	Penicillins, cephalosporins, imipenem aztreonam(beta-lactams) , , vancomycin, Antifungals
Inhibition of protein synthesis 50S 30S	 Chloramphenicol, erythromycin, clindamycin, linezolid, Tetracyclines and aminoglycosides
Inhibition of nucleic acid synthesis	Sulfonamides, trimethoprim, Quinolones,(e.g.ciprofloxacin) Rifampin
Alteration of cell membrane function	Polymyxin, daptomycin & Antifungals(Amphotericin B, nystatin)
Other mechanisms of action	Isoniazid, metronidazole, Antifungals

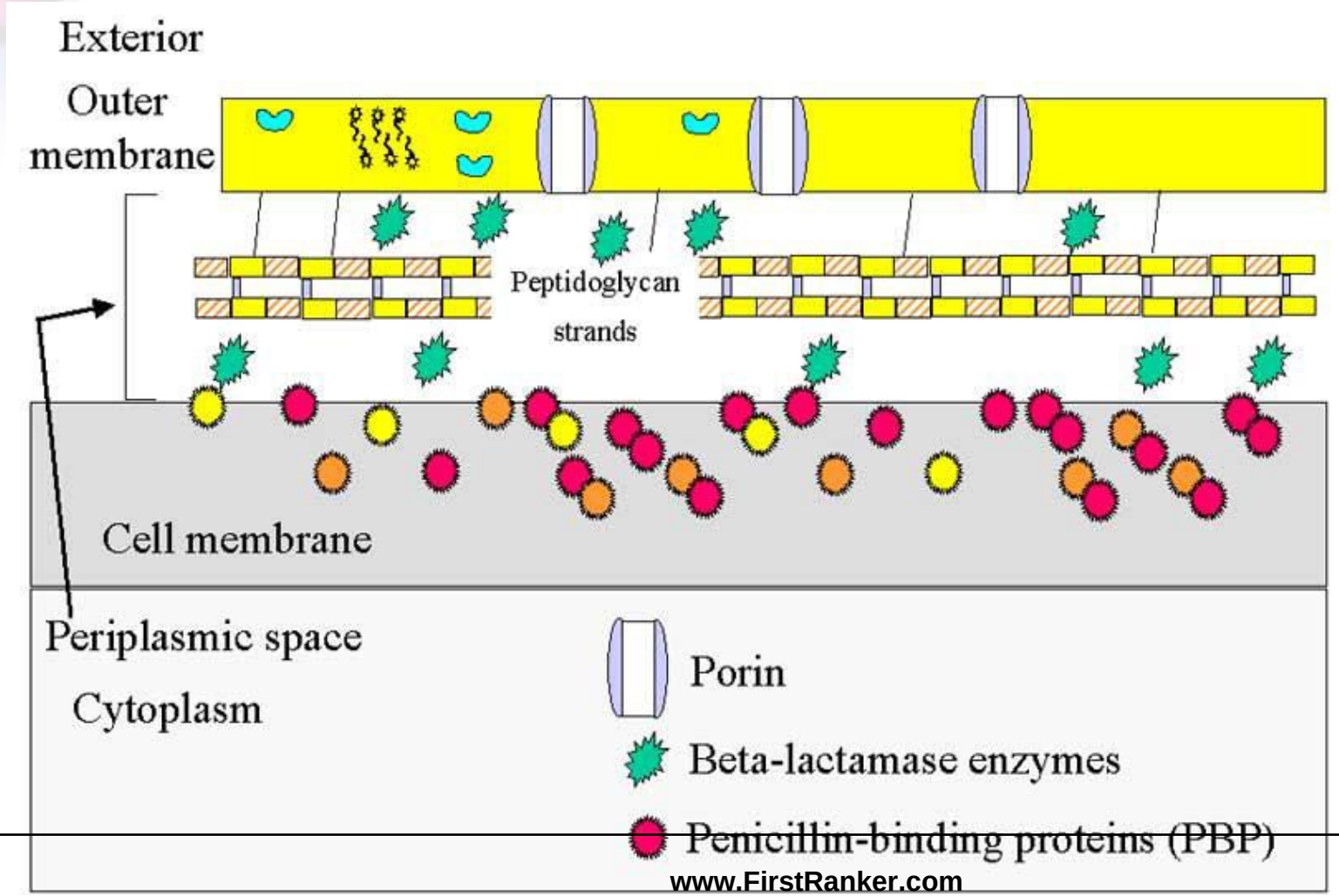
Classifications

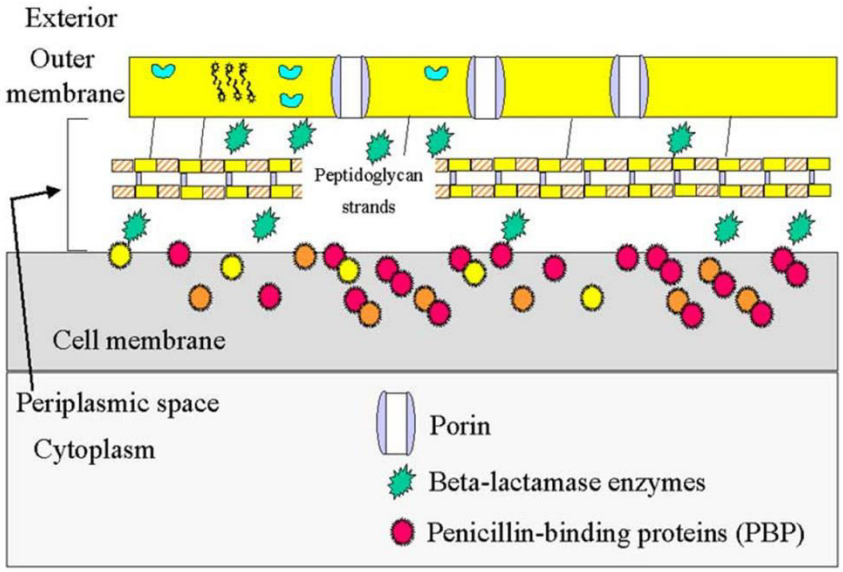
- Penicillins }
- Cephalosporins (ceftriaxone) } Beta-lactams
- Cabapenems }
- Glycopeptides (vancomycin)
- Sulfonamides (septran)
- Tetracyclines
- Macrolides (Erythromycin, Azithromycin, & clarithromycin)
- Aminoglycosides(Gentamicin)
- Quinolones (ciprofloxacin)

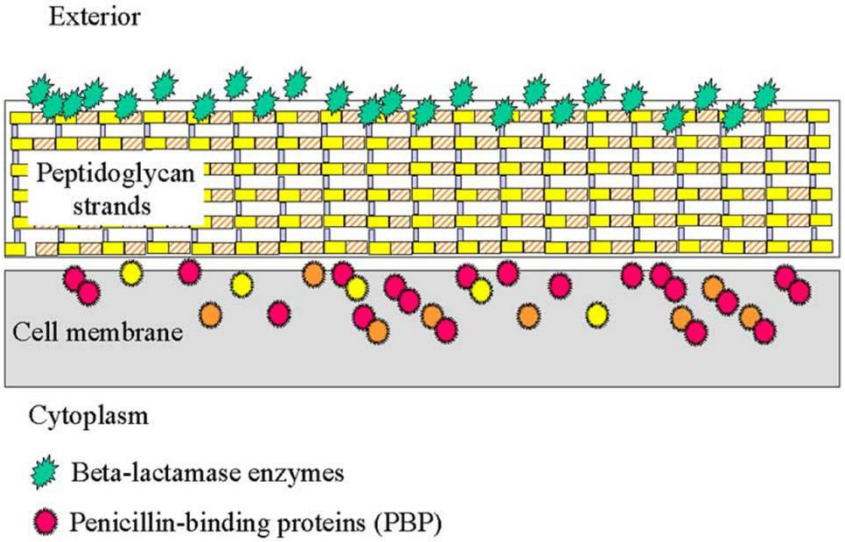
Antibiotics that Inhibit Cell Wall Synthesis

Bacterial cell wall









- Prokaryotes differ from eukaryotes by having a cell wall that includes a peptidoglycan layer.

- Peptidoglycan consists of multiple amino-sugars that alternate NAG and NAM which are cross linked to form a lattice.
- Cross-linking is essential to resist the high internal osmotic pressures
- Peptidoglycan components manufactured intracellularly and transported across the cell membrane, where they link by transpeptidation.

Penicillins

- 1.They bind to penicillin binding proteins (PBPs).on the bacterial cell wall
- Inhibit transpeptidation of the peptidoglycan layer.
- 2.Autolytic enzymes called murein hydrolases (murein is a synonym for peptidoglycan) are activated in penicillin-treated cells and degrade the peptidoglycan
- Penicillin-treated cells die by rupture as a result of the influx of water
- Act only on growing cells

VIDEO

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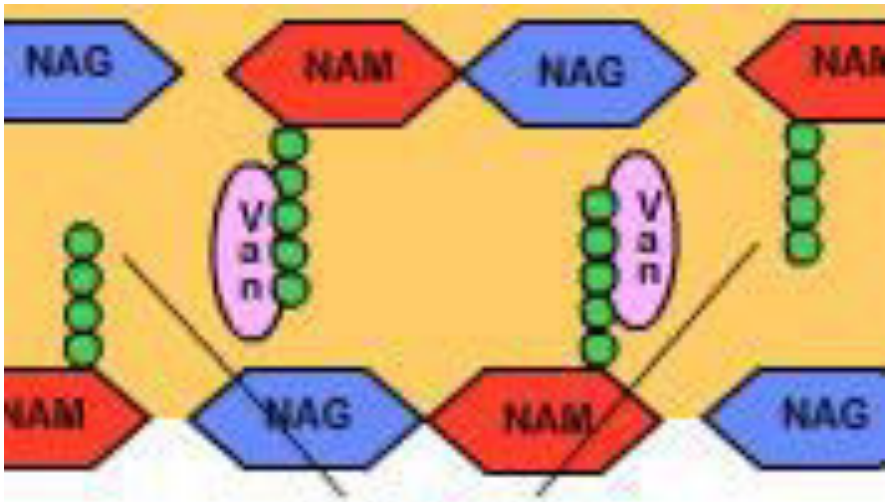
Other Beta -lactams

- Cephalosporins,, carbapenems & Aztreonam are beta-lactam drugs that act in the same manner as penicillins; i.e., they are bactericidal agents that inhibit the cross-linking of peptidoglycan.

Vancomycin

- A glycopeptide that inhibits cell wall synthesis by blocking transpeptidation but by a mechanism different from that of the β-lactam drugs. It binds directly to the D-alanyl-D-alanine portion of the pentapeptide, which blocks the transpeptidase from binding, whereas the beta-lactam drugs bind to the transpeptidase itself.

Vancomycin m.o.a



Summary of antibiotics acting on cell wall

- Could be due to
  - Inhibition of enzymes
  -Complexing with the growing part of peptidoglycan

- http://www.microbelibrary.org/images/spencer/spencer_cellwall.html

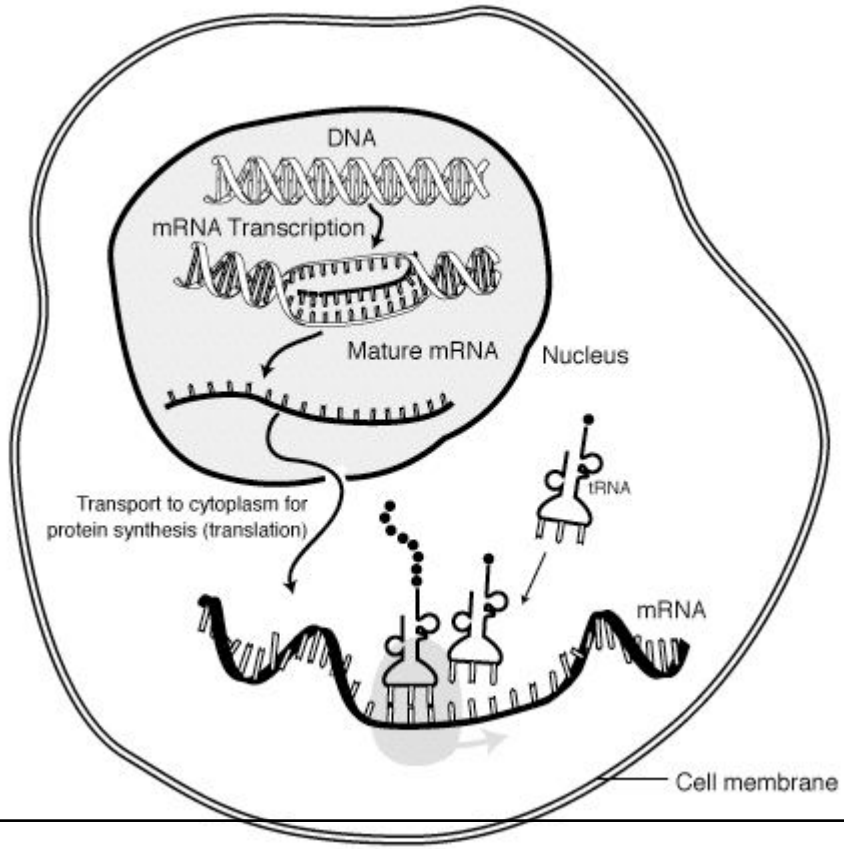
Inhibition of fungal cell wall synthesis

- By inhibiting the enzyme that synthesizes beta –glucan, a component of fungal cell walls

Antimicrobial agents affecting Bacterial Protein Synthesis

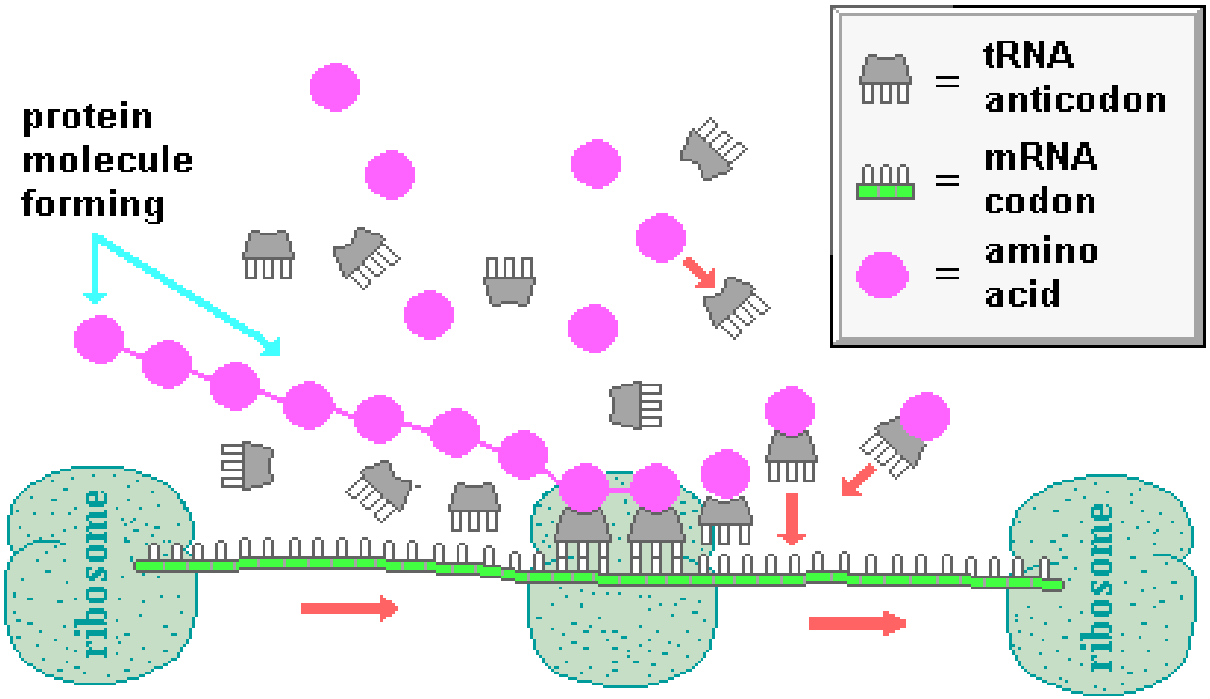
Normal protein synthesis in Bacteria

- Transcription
- Translation



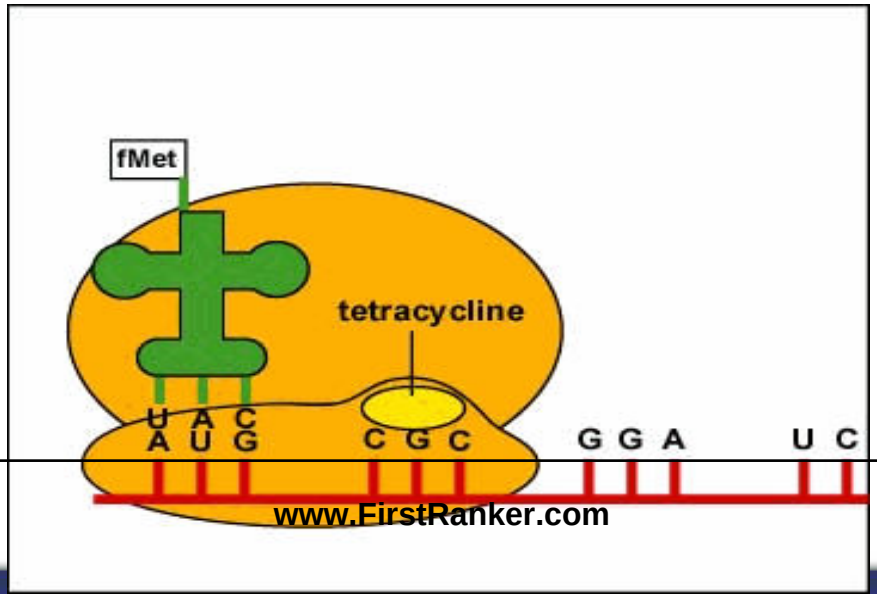
- **Transcription** occurs in the cell nucleus, where the DNA is held. The DNA is "unzipped" by the enzyme helicase, leaving the single nucleotide chain open to be copied. RNA polymerase reads the DNA strand , while it synthesizes a single strand of messenger RNA. The single strand of mRNA leaves the nucleus and migrates into the cytoplasm.
- The synthesis of proteins is known as **translation**. Translation occurs in the cytoplasm, where the ribosomes are located. Ribosomes are made of a small and large subunit that surround the mRNA. In translation, messenger RNA (mRNA) is decoded to produce a specific polypeptide. This uses an mRNA sequence as a template to guide the synthesis of a chain of amino acids that form a protein.

Protein synthesis



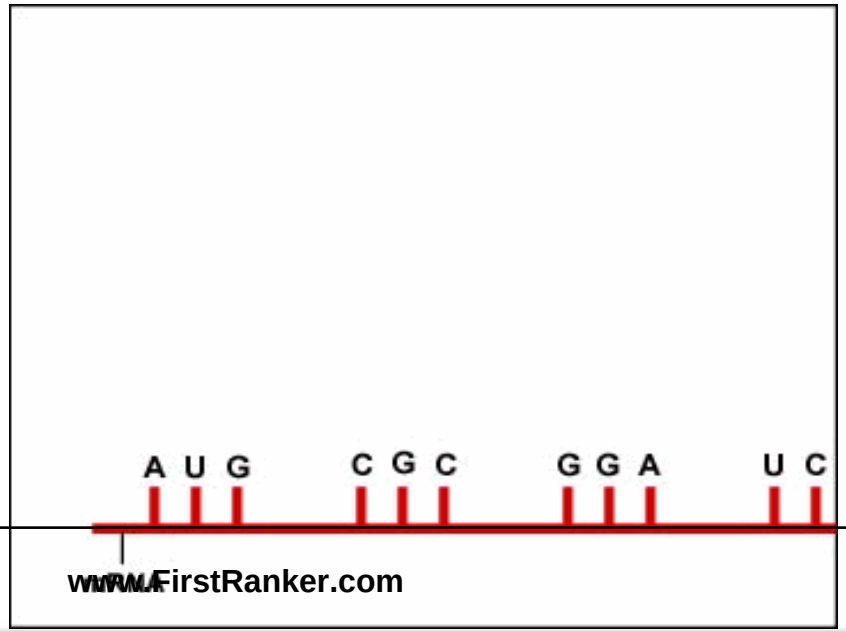
Tetracyclines

- They block protein synthesis by competing with tRNA for the A site of the ribosome/ mRNA complex.



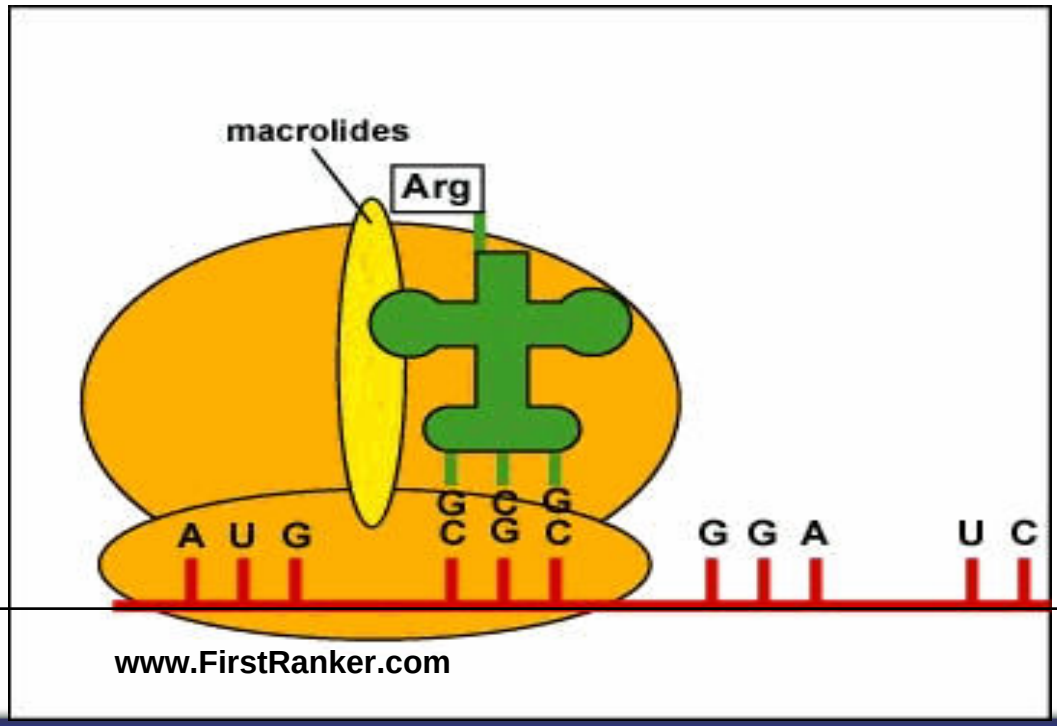
Aminoglycosides

- Bind to 30S subunit and prevent complexing of the 50S subunit. (compare with normal)



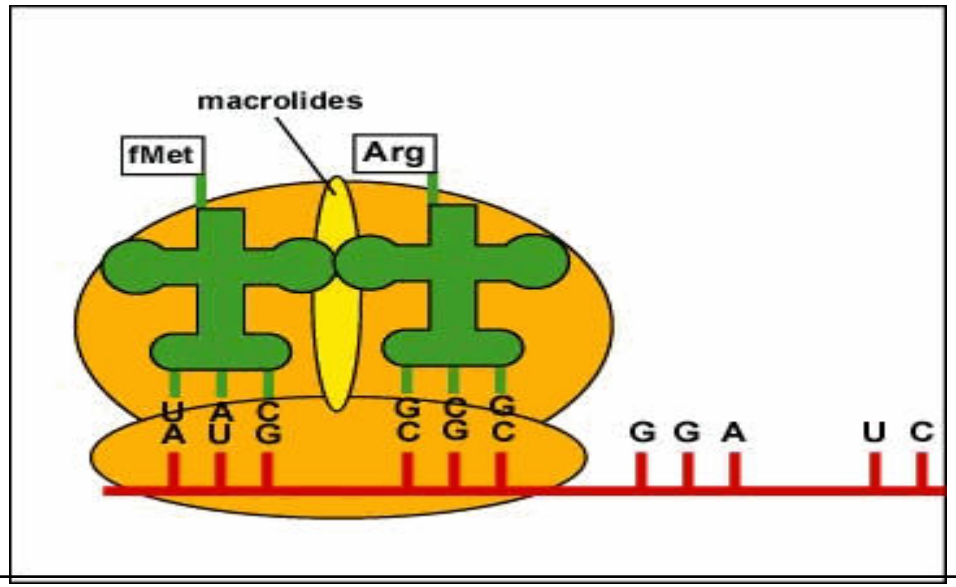
Erythromycin

- Inhibits translocation of ribosome along mRNA chain



Chloramphenicol

- Binds to the 50S subunit at same site as erythromycin, and inhibits transpeptidation



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INHIBITION OF NUCLEIC ACID SYNTHESIS

- 1.Inhibition of precursor synthesis

  e.g Sulphonamides & Trimethoprim

  inhibit synthesis of tetrahydrofolic acid which is required for synthesis of nucleic acid precursors A, G, T

INHIBITION OF NUCLEIC ACID SYNTHESIS cont----

- 2. Inhibition of DNA synthesis by inhibiting DNA gyrase an enzyme which unwinds DNA strands for replication e,g Fluoro-Quinolones

Alteration of Bacterial Cell Membranes

- Few antimicrobial compounds act on the cell membrane because the structural and chemical similarities of bacterial and human cell membranes make it difficult to provide sufficient selective toxicity
- E.g Polymyxins

Alteration of Fungal Cell Membranes

- Human cells have got cholesterol in their membranes while fungi have got ergosterol
- E.g Amphotericin B -It disrupts the cell membrane of fungi because of its affinity for ergosterol

www.FirstRanker.com

Additional drug mechanisms

www.FirstRanker.com

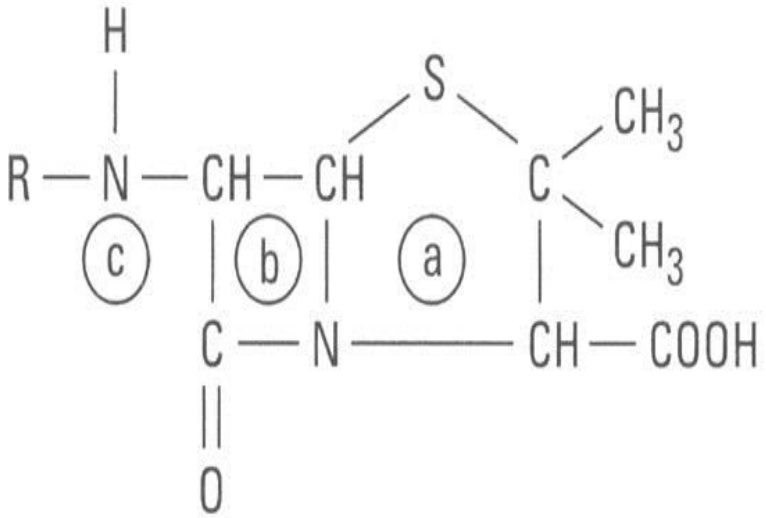
Isoniazid

- Bactericidal drug for Mycobacterium tube-rculosis (MTB) and other mycobacteria
- Inhibits mycolic acid synthesis (a part of Mycobacterial cell wall)

Some important antibiotics

Beta-Lactam Antibiotics

- So called because they have a beta-lactam ring.
- Penicillins, Cephalosporins, Carbapenems and monobactams.



Penicillins

- Available in 3 forms

  -Aqueous Pen.-rapidly metabolized

  -Procaine Pen- less painful

  -Benzathine Pen-very slowly metabolized(depot pen.)

Disadvantages of Penicillins

- Limited effect against G-ves
- Hydrolysis by gastric acid- no oral use
- Inactivation by beta lactamase enzymes
- Hypersensitivity (1-10%), Anaphylaxis(0-5%)

Cephalosporins

- Cephalosporins are beta-lactam drugs that act in the same manner as penicillins. The structures, however , are different:
- Cephalosporins have a 6-membered ring adjacent to the beta-lactam ring ,while penicillins have a 5-membered ring
- Bactericidal
- Products of the mould cephalosporium
- Five generations. 1st active against GPCs, 2, 3, 4 more against G-ves

Cephalosporins cont---

- Few allergic reactions
- Some are oral, but most are given parentally.
- Wide distribution after absorption
- E.gs Cefuroxime, cefotaxime and ceftriaxone
- Broadspectrum, active against most Gram +ve's, some Gram –ve activity

Carbapenems

- Carbapenems are β-lactam drugs that are structurally different from penicillins and cephalosporins
- Wide bactericidal activity against many gram -positive, gram -negative, and anaerobic bacteria
- Eg. Imipenem, Meropenem etc

Glycopeptides

- E.gs Vancomycin
- Bactericidal for Gram positives esp MRSA

Tetracyclines

- Broad spectrum, originally derived from *Streptomyces*. More recent compounds are semi-synthetic or synthetic
- Bacteriostatic action against gram +ve/-ve and some protozoa
- Absorbed orally
- Tetracycline, Vibramycin, Minocycline

Tetracyclines

- Effectiveness reduced by
  - Dairy products
  - Antacids
  - Iron
- Contraindicated in pregnancy & children (discolor teeth ,may slow fetal skeletal development

Aminoglycosides

- Poor oral absorption
- No oral forms, only IV
- TOXICITY cautions
  - Nephro
  - oto
- Bactericidal action against GNRs like *Pseudomonas, E.coli, Klebsiella*
- Poor entry into CSF

Aminoglycosides

- Gentamicin
- Kanamycin
- Neomycin
- Streptomycin
- Amikacin

Chloramphenicol

- Active against many gram +ve & gram-ves
- Inhibits protein synthesis to some extent in mitochondria of human cells
- Bone marrow depressant (dose dependant)
- Aplastic anemia (idiosyncratic)

Fluoro-Quinolones

- 5 generations
- Newer forms (ciprofloxacin, ofloxacin and levofloxacin) have wider activity
- Used for RTI, UTI, GIT, Skeletal & soft tissue infections
- Contraindicated in pregnancy & young child

  -ren, as it damages growing cartilage

Sulphonamides & Trimethoprim

- Bacteriostatic, good against gram –ve's
- Sulphonamides & Trimethoprim are two drugs but are used together for synergistic effect.
- E.g Septran
- Side Effects=Anemia, thrombocytopenia, Photosensitivity(Avoid tanning , Avoid sunlight)

Sulfonamides

- Bacteriostatic

Used to Treat:

- UTI
- Pneumocystis jiruveci pneumonia (PCP)
- URIs
- Otitis media
- Often in combination
  - Bactrim, Septra

Macrolides

- Bacteriostatic drugs with a wide spectrum of activity .
- Erythromycin, Azithromycin, Clarithromycin
- Given in Strept. infections in Penicillin allergic pts.

Clindamycin

- Bacteriostatic drug against anaerobes
- Important side effect of clindamycin is pseudomembranouscolitis (suppression of the normal flora of the bowel by the drug and overgrowth of a drug-resistant strain of *Clostridium difficile*) causing severe bloody diarhea

Rifampicin

- Used in Tuberculosis & close contacts of meningitis
- Not given alone as rapid resistance develops

Isoniazid

- Bactericidal drug for (MTB) and other mycobacteria
- Effective against the organisms residing within macrophages
- Side effect = Liver toxicity

Metronidazole (Flagyl)

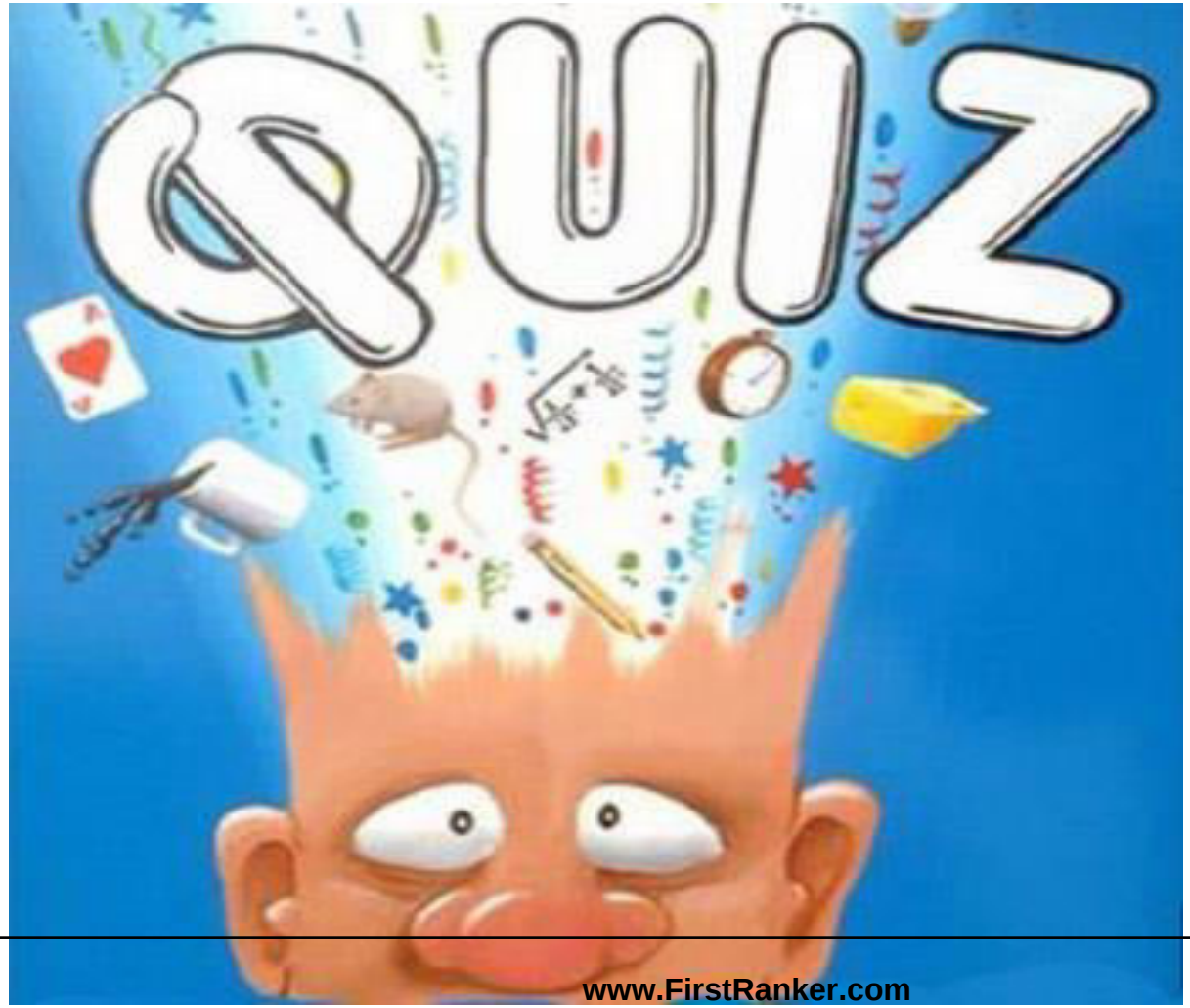
- Bactericidal against anaerobic bacteria.
- It is also effective against certain protozoa such as Giardia and Trichomonas .

Antifungals

- Amphotericin B has significant renal toxicity; measurement of serum creatinine levels is used to monitor the dose
- Nystatin, Azoles (Fluconazole, ketoconaz-ole,voriconazole, posaconazole, and itraconazole) used in local and systemic fungal diseases

Nursing

- Instruct pt to take meds for full length of time – do not stop when feeling better
- Assess for s/s of superinfection



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live, nonpathogenic bacteria. Provide colonization resistance by which the nonpathogen excludes the pathogen from binding sites on the mucosa.

Targets for antibiotic action

- cell wall
- cell membrane
- protein synthesis
- nucleic acid

Mechanism of Action of Important Antibacterial and Antifungal Drugs

- Inhibition of cell wall synthesis

  Penicillins, cephalosporins, imipenem , aztreonam , vancomycin, Antifungals

- Inhibition of protein synthesis

  50S Chloramphenicol, erythromycin, clindamycin, linezolid,

  30S Tetracyclines and aminoglycosides

Normal protein synthesis in Bacteria-Steps

- Transcription

mRNA is formed from DNA in the nucleus

- Translation

The synthesis of proteins is known as translation. Translation occurs in the cytoplasm

- Micro exam 3 quizlet