Antimicrobial agent

- Antimicrobial derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms.
- "antimicrobials" include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal)
- This is not synonymous with antibiotics, derived from the Greek word anti (against) and biotikos (concerning life).
- "Antibiotic" refers to substances produced by microorganisms that act against another microorganism.
- "antibacterials", being the largest and most widely known and studied class of antimicrobials, is often used interchangeably with the term "antimicrobials"

Classification of antimicrobial

Antibiotics are classified by several ways:

- Chemical structure
- Mechanism of action
- Types of organisms against which primarily active
- Spectrum of activity
- Type of action
- Sources of antibiotics

A. Chemical structure

1. *Sulfonamides and related drugs*: Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. *Diaminopyrimidines:* Trimethoprim, Pyrimethamine.
3. *Quinolones:* Nalidixic acid, Norfloxacin, Ciprofloxacin, Gatifloxacin, etc.
4. *β-Lactam antibiotics:* Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. *Tetracyclines:* Oxytetracycline, Doxycycline, etc.
6. *Nitrobenzene derivative:* Chloramphenicol.
7. *Aminoglycosides:* Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. *Macrolide antibiotics:* Erythromycin, Clarithromycin, Azithromycin, etc.
9. *Lincosamide antibiotics:* Lincomycin, Clindamycin.
10. *Glycopeptide antibiotics:* Vancomycin, Teicoplanin.
11. *Oxazolidinone:* Linezolid.
12. *Polypeptide antibiotics:* Polymyxin-B, Colistin, Bacitracin, Tyrothricin.
13. *Nitrofuran derivatives:* Nitrofurantoin, Furazolidone.
14. *Nitroimidazoles:* Metronidazole, Tinidazole, etc.
15. *Nicotinic acid derivatives:* Isoniazid, Pyrazinamide, Ethionamide.
16. *Polyene antibiotics:* Nystatin, Amphotericin-B, Hamycin.
17. *Azole derivatives:* Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
18. *Others:* Rifampin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin.

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B. Mechanism of action

1. *Inhibit cell wall synthesis*: Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.
2. *Cause leakage from cell membranes*: Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes—Amphotericin B, Nystatin, Hamycin.
3. *Inhibit protein synthesis:* Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.
4. *Cause misreading of m-RNA code and affect permeability:* Aminoglycosides—Streptomycin, Gentamicin, etc.
5. *Inhibit DNA gyrase:* Fluoroquinolones—Ciprofloxacin and others.
6. *Interfere with DNA function:* Rifampin, Metronidazole.
7. *Interfere with DNA synthesis:* Acyclovir, Zidovudine.
8. *Interfere with intermediary metabolism:* Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Ethambutol.

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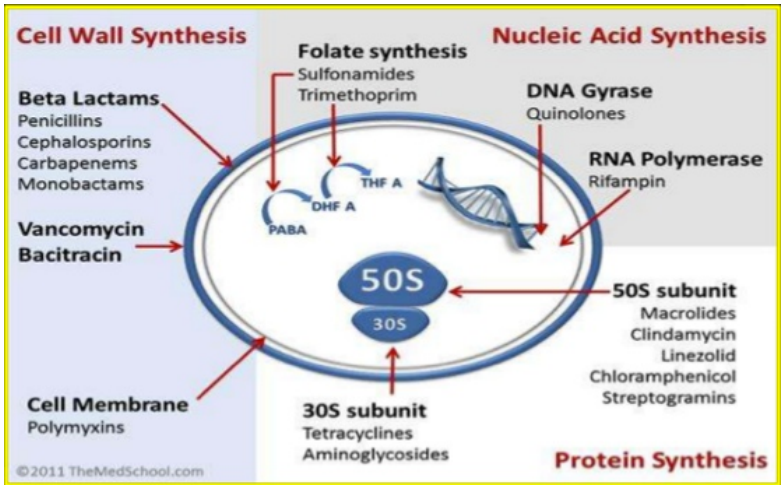
Action of Antibiotics on bacterial cell



C. Type of organisms against which primarily active

1. *Antibacterial:* Penicillins, Aminoglycosides, Erythromycin, etc.
2. *Antifungal*: Griseofulvin, Amphotericin B, Ketoconazole, etc.
3. *Antiviral:* Acyclovir, Amantadine, Zidovudine, etc.
4. *Antiprotozoal:* Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
5. *Anthelmintic:* Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

D. Spectrum of activity

Narrow-spectrum	*Broad-spectrum*
Penicillin G	Tetracyclines
Streptomycin	Chloramphenicol
Erythromycin	

E. Type of action

Primarily bacteriostatic

Sulfonamides	Erythromycin
Tetracyclines	Ethambutol
Chloramphenicol	Clindamycin
	Linezolid

stops bacteria from multiplying by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism

Primarily bactericidal

Penicillins	Cephalosporins
Aminoglycosides	Vancomycin
Polypeptides	Nalidixic acid
Rifampin	Ciprofloxacin
Isoniazid	Metronidazole
Pyrazinamide	Cotrimoxazole

kills the bacteria generally by either interfering with the formation of the bacterium's cell wall or its cell contents.

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F. Antibiotics are obtained from:

Fungi

Penicillin	Griseofulvin
Cephalosporin	

Bacteria

Polymyxin B	Tyrothricin
Colistin	Aztreonam
Bacitracin	

Actinomycetes

Aminoglycosides	Macrolides
Tetracyclines	Polyenes
Chloramphenicol	

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Problem arise with the use of Antimicrobial Agent

1. Toxicity

Local: Gastric irritation, pain and abscess formation at the site of i.m. injection

Systemic

Aminoglycosides : 8th cranial nerve and kidney toxicity.

Tetracyclines : liver and kidney damage.

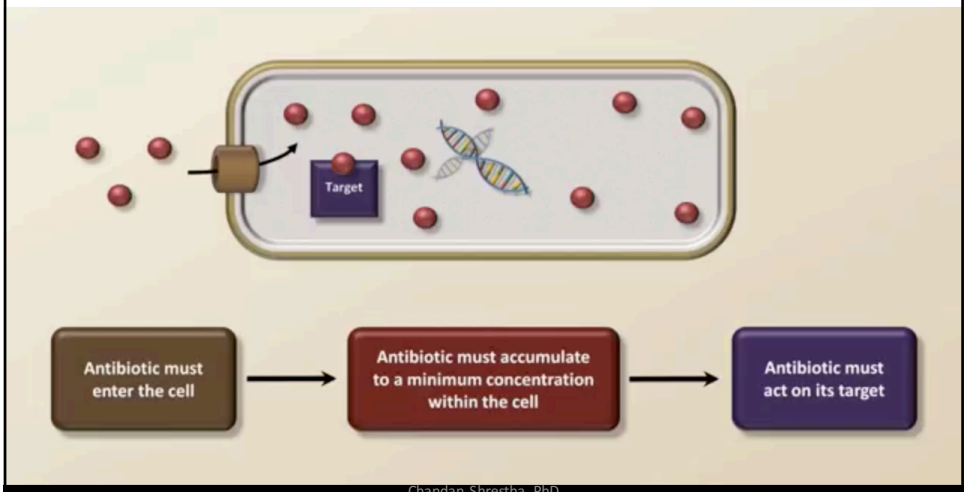
Chloramphenicol : bone marrow depression.

2. Hypersensitivity reaction
3. Drug resistance
4. Superinfection
5. Nutritional deficiencies

Antimicrobial resistance

- Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
- Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g. antibiotics), antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.

How does antibiotics works?



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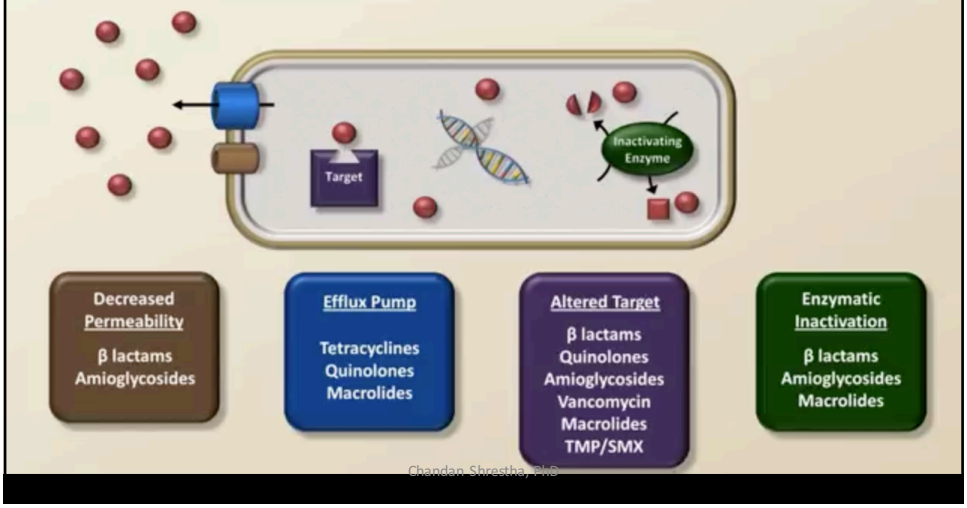
Mechanisms of Antibiotic Resistance



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Methods of avoiding resistance

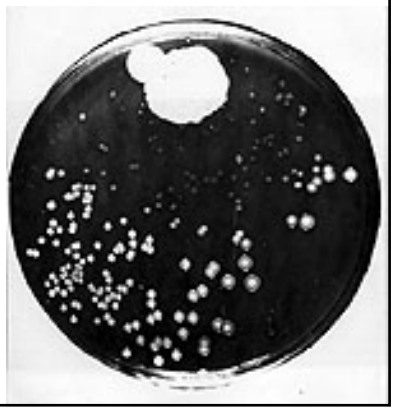
- Avoiding the unnecessary use of antibiotics.
- Using antibiotics in full adequate dosage.
- If unnecessary, avoiding the topical use of antibiotics for a prolonged period.
- Whenever possible, using the narrow spectrum antibiotics.
- If necessary, using a combination drug regimen and using the drugs in turn.

Discovery of antibiotics

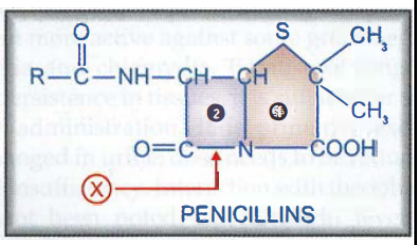
"One sometimes finds what one is not looking for"

(Sir Alexander Fleming)

In 1928, fungus (Penicillium notatum) had destroyed bacteria in a staphylococcus culture plate.



Antibiotics: Penicillins



- First introduced in the 1940s
- Bactericidal: inhibit cell wall synthesis
- Broad spectrum antibiotic: Kill a wide variety of bacteria
- Also called "beta-lactams"
- Bacteria produce enzymes capable of destroying penicillins. These enzymes are known as *beta-lactamases*.
- As a result, the medication is not effective.
- *Beta lactamase inhibitor*-chemicals bind with beta-lactamase and prevent the enzyme from breaking down the penicillin.

Antibiotics: Penicillins

1) Narrow spectrum penicillins- Penicillin V, penicillin G
2) Broad Spectrum Penicillins (aminopenicillin)- Amoxicillin, Ampicillin
3) Penicillinase-resistant Penicillin (anti-staphyloccocal penicillins)- Cloxacillin, Nafcillin, Methicillin, Dicloxacillin
4) Extended-Spectrum penicillins (Anti-pseudomonal penicillins)- Carbenicillin, Mezlocillin, Piperacillin, Ticacillin

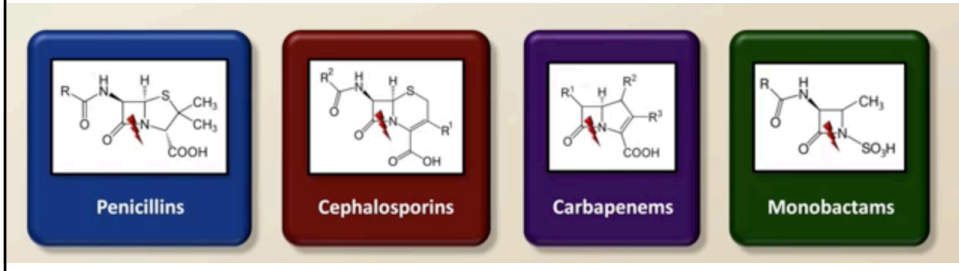
Beta-lactamase inhibitors- Clavulanic acid, Sulbactam, Tazobactam

Penicillins: Mechanism of Action

- Penicillins enter the bacteria via the cell wall.
- Inside the cell, they bind to penicillin-binding protein.
- Once bound, normal cell wall synthesis is disrupted.
- Result: bacteria cells die from cell lysis.

β-lactamases inhibitors

- β lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring.



- Three inhibitors of this enzyme clavulanic acid, sulbactam and tazobactam are available for clinical use.

Penicillins: Therapeutic Uses

- Prevention and treatment of infections caused by susceptible bacteria, such as:
  - gram-positive bacteria
  - Streptococcus, Enterococcus, Staphylococcus species

Ampicillin

Uses

- UTI
- Meningitis
- Typhoid fever
- Chronic bronchitis
- Gonorrhoea

Dose: 250-500 mg qid

Amoxycillin

Uses

- UTI/ RTI
- Meningitis
- Typhoid fever
- Otitis media
- Gonorrhoea

Dose: 250-500 mg tid

Route: oral/im/iv

Penicillins: Adverse Effects

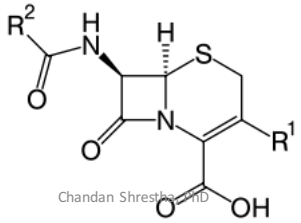
- Allergic reactions occur in 0.7% – 8% of treatments: Urticaria, pruritus, angioedema
- 10% of allergic reactions are life-threatening, and 10% of these are fatal
- Common side effects: nausea, vomiting, diarrhea, abdominal pain

Penicillin: Nursing consideration

- Take on an empty stomach
  - Food slows absorption
  - Acids in fruit juices or colas could deactivate the drug
- Use full course of antibiotic
- No self treatment
- Warning: Hypersensitivity reaction

Antibiotics: Cephalosporins

- Semisynthetic derivatives from a fungus
- Structurally and pharmacologically related to penicillins
- Bactericidal action
- Broad spectrum
- MOA similar to penicillins (inhibition of bacterial cell wall synthesis)
- These have been conventionally divided into 4 generations.



Antibiotics: Cephalosporins

- **First Generation:** *cefadroxil*, *cephalexin*, cephradine, *cefazolin*, cephalothin, cephapirin
- **Second Generation:** *cefaclor*, cefonicid, cefprozil, ceforanide, Cefamandole, cefmetazole, cefoxitin, cefotetan, *cefuroxime*
- **Third Generation**: *Cefixime*, ceftizoxime, *cefpodoxime proxetil*, *ceftriaxone*, cefoperazone, ceftazidime, *cefotaxime*
- **Fourth Generation**: *Cefepime*, cefpirome
- **Fifth Generation**: Ceftozoline, Ceftaroline, ceftobiprole

First generation cephalosporins	
Parenteral	*Oral*
Cephalothin*	Cephalexin
Cefazolin	Cephradine
	Cefadroxil
Second generation cephalosporins	
Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil
Third generation cephalosporins	
Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	Ceftamet pivoxil
Fourth generation cephalosporins	
Parenteral	
Cefepime	
Cefpirome	

Highly active against gram +ve but weaker against gram -ve

More active against gram -ve

highly augmented activity against gram -ve

similar to that of 3rd generation compounds, but is highly resistant to β-lactamases

Cephalosporin: Uses

- As alternative to penicillin
- RTI
- UTI
- Meningitis
- Typhoid fever
- gonorrhoea
- Skin infection

Cephalosporin: Adverse effect

- Anaphylactic reaction
- Skin rashes
- Nausea
- Vomiting
- Diarrhoea
- Nephrotoxicity
- Pain in the site of injection

Cephalosporins- Nursing consideration

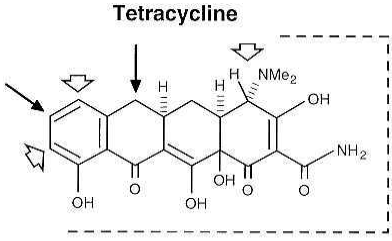
- Alert if a patient allergic to penicillins is receiving a cephalosporin prescription.
- All of the cephalosporins look alike when written in the generic form. Watch for dosing and indications for use.

Carbapenems

- Beta lactam antibiotics
- Are beta lactamase resistant and are drug of choice for enterobacter klebsiella
- Active against gram positive cocci, gram negative cocci as well as anaerobes
- Drugs- Imipenem, meropenem, ertapenem
- Imipenem is inactivated by renal dehydropeptidase so it is combined with cilastatin, a dehydropeptidase inhibitor)

Antibiotic- Tetracycline

- Tetracycline is a group of broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.
- They are active against gram positive and gram negative bacteria including anaerobes, rickettsiae, chlamydiae, mycoplasmas and L forms; and against some protozoa.
- Natural and semi-synthetic
- Obtained from cultures of Streptomyces



Tetracycline- Classification

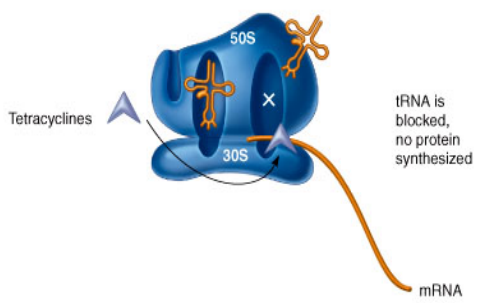
1. Short acting (t1/2 = 6-8 hr)
   Tetracycline, Chlortetracycline, Oxytetracycline

2. Intermediate acting (t1/2 = 12 hr)
   Demeclocycline, Methacycline, Lymecycline

3. Long acting (t1/2 = 16-18 hr)
   Doxycycline, Minocycline

Tetracycline- Mechanism of Action

✓ Reversibly bind to 30S subunit and inhibit binding of aminoacyl- t-RNA to the acceptor site on the ribosome→ inhibit protein synthesis.



Tetracycline: Uses

- Mycoplasma chlamydia and Rickettsia
- Acne vulgaris
- RTI
- UTI
- Cholera
- Staphylococcal and streptococcal infection

Tetracycline- Adverse effect

- Nausea, vomiting, diarrhoea, epigastric pain
- Phototoxicity
- Discoloration of teeth
- Bone marrow depression
- Kidney and liver may damage
- Allergic reaction
- Superinfection

Tetracycline: Precautions

- Tetracyclines should not be used during pregnancy, lactation and in children.
- They should be used cautiously in renal or hepatic insufficiency.
- Preparations should never be used beyond their expiry date.
- Do not mix injectable tetracyclines with penicillin- inactivation occurs.
- Do not inject tetracyclines intrathecally

Tetracycline: Nursing consideration

- Avoid antacids to avoid chelation with minerals
- Photosensitization
- To be avoided by pregnant women and children
- Expired drugs are dangerous

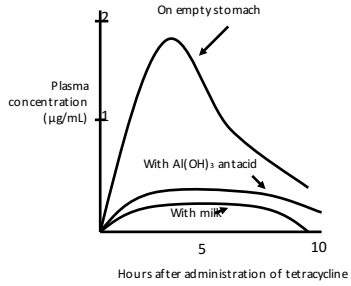
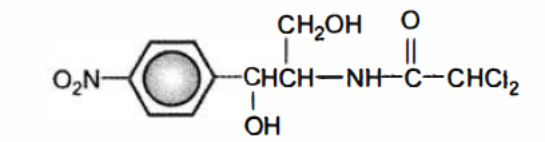


Fig: Effect of antacid and milk on absorption of tetracycline

Antibiotics- Chloramphenicol

- Chloramphenicol is a broad spectrum bacteriostatic antibiotics that are active against both aerobic and anaerobic gram positive and gram negative organisms.
- It is also active against rickettsiae but not chlamydiae.
- Chloramphenicol was initially obtained from *Streptomyces venezuelae* in 1947 from a soil sample collected in Venezuela.



CHLORAMPHENICOL

Chloramphenicol- MOA

- Inhibits protein synthesis
- It binds reversibly to the 50S subunit of bacterial ribosome.
- It inhibits the peptidyl transferase step of protein synthesis.

Chloramphenicol- Uses

- Typhoid fever
- Meningitis
- Haemophillus influenza infection
- Whooping cough
- Local application: eye/ear drop

Chloramphenicol- Adverse Effects

- Bone marrow depression
- Aplastic anemia
- Peripheral and optic neuritis
- Gray baby syndrome
- Nausea, vomiting, diarrhoea
- Hypersensitivity reactions

Antibiotic- Aminoglycosides

- Natural and semi-synthetic
- Produced from Streptomyces
- Poor oral absorption; no PO forms
- Very potent antibiotics with serious toxicities
- Bactericidal
- Kill mostly gram-negative; some gram-positive also

Antibiotic- Aminoglycosides

Systemic aminoglycosides

Streptomycin	Amikacin
Gentamicin	Sisomicin
Kanamycin	Netilmicin
Tobramycin	

Topical aminoglycosides

Neomycin	Framycetin

Aminoglycosides- MOA

- The aminoglycosides are bactericidal antibiotics all having the same general pattern of action which is described in two main steps;

✓ Transport of the aminoglycoside through the bacterial cell wall and cytoplasmic membrane

✓ Binding to ribosomes resulting in inhibition of protein synthesis

Aminoglycosides: Adverse Effects

- Ototoxicity and nephrotoxicity are the most significant
- Neuromuscular blockade

Systemically used aminoglycoside	Ototoxicity		Nephrotoxicity
	vestibular	cochlear	
1. Streptomycin	++	±	+
2. Gentamicin	++	+	++
3. Kanamycin	+	++	++
4. Tobramycin	++	+	+
5. Amikacin	+	++	++
6. Sisomicin	++	+	++
7. Netilmicin	+	+	++

0.5 g i.m. BO-TOS

15 mg/kg/day in 1-3 doses; UTI -7.5 mg/kg/ day.

Macrolide: Erythromycin

- It was isolated from Streptomyces erythreus in 1952.
- Since then it has been widely employed, mainly as alternative to penicillin.
- Bacteriocidal at high concentration but bacteriostatic at low concentration.
- MOA: Erythromycin acts by inhibiting bacterial protein synthesis. lt combines with 50S ribosome subunits and interferes with 'translocation'.
- Dose: 250-500mg qid

Erythromycin: Uses

1. As an alternative to penicillin

- Diptheria
- Tetanus
- Syphilis and gonorrhoea

2. As a first choice drug for

- Atypical pneumonia caused by Mycoplasma pneumoniae
- Whooping cough
- Chancroid

Erythromycin: Adverse effect

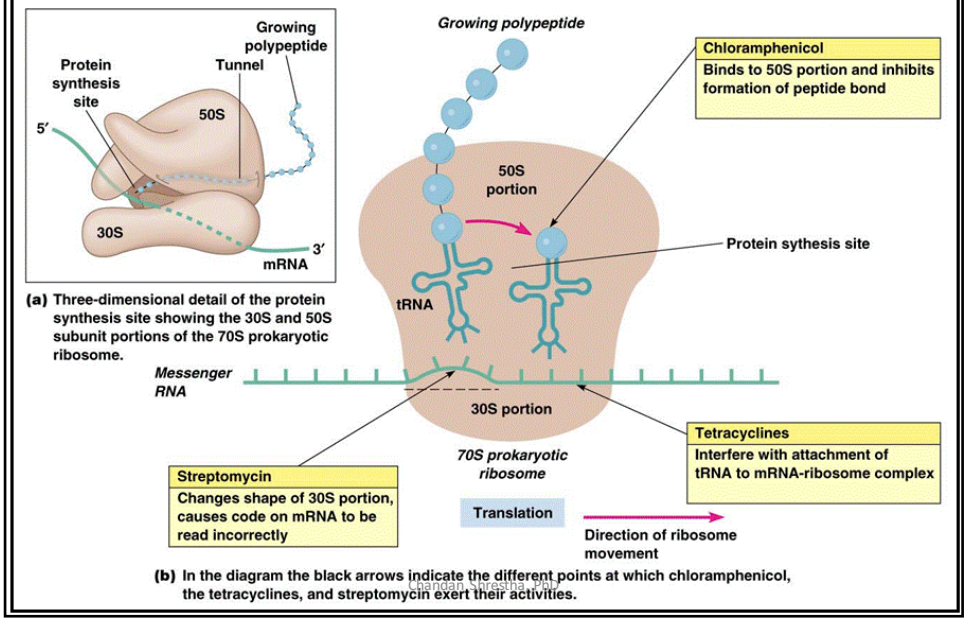
- Gastrointestinal: Nausea, Vomiting, Diarrhoea
- Hypersensitivity
- Very high doses of erythromycin have caused reversible hearing impairment.

Newer Macrolide

- Roxithromycin (150mg BD)
- Clarithromycin (250-500 mg BD)
- Azithromycin (500 mg OD)

Macrolides' Nursing consideration

Although most antibiotics should be taken on an empty stomach, erythromycins usually cause severe GI distress, so should be taken with food



Antibiotics: Sulfonamides

- One of the first groups of antibacterial agents
- Bacteriostatic action
- Prevent synthesis of folic acid required for synthesis of purines and nucleic acid
- Does not affect human cells or certain bacteria—they can use preformed folic acid

Sulfonamide: Classification

1. ***Short acting*** *(4–8 hr)*: Sulfadiazine
2. ***Intermediate acting*** *(8–12 hr)*: Sulfamethoxazole
3. ***Long acting*** *(~7 days)*: Sulfadoxine, Sulfamethopyrazine
4. ***Special purpose sulfonamides***: Sulfacetamide sod., Mafenide, Silver sulfadiazine, Sulfasalazine

Sulphonamide: Uses

- Simple UTI
- Meningitis
- Bacillary dysentry
- Tonsilitis
- Pneumonia
- Opthalmic use

Sulphonamide: Adverse Effect

Side effect

- Nausea
- Skin rashes
- Crystal urea
- Vomiting
- Blood disorders

Toxic effect

- Drug fever
- Kernicterus
- Foetus distress
- Stevens- Johnson syndrome
- Exofoliative dermatitis

Cotrimoxazole: MOA

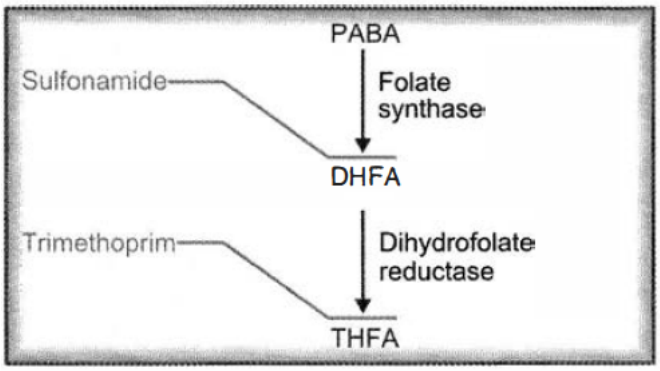


Fig. 50.1: Sequential block in bacterial folate metabolism
PABA—Para aminobenzoic acid; DHFA—Dihydrofolic acid; THFA—Tetrahydrofolic acid

Cotrimoxazole→ sulfametaxazole: Trimethoprin (5:1)

Cotrimoxazole: Uses

- UTI
- Respiratory Tract Infection
- Bacterial diarrhoeas and dysentery
- typhoid

Sulfonamides' Dispensing Issues

- Avoid the sun
- Maintain adequate fluid intake

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Antibiotic: Quinolone

- are broad-spectrum antibiotics with particular activity against gram-negative organisms, especially *Pseudomonas aeruginosa* that inhibit the DNA gyrase.
- Bactericidal
- Alter DNA of bacteria causing death
- Do not affect human DNA.

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Quinolones: Classification

Classification	Agents	Antimicrobial spectrum
First generation	Nalidixic acid Cinoxacin	Gram-negative organisms (but not Pseudomonas species)
Second generation	Norfloxacin Lomefloxacin Enoxacin Ofloxacin Ciprofloxacin	Gram-negative organisms (including Pseudomonas species), some gram-positive organisms (including *Staphylococcus aureus* but not *Streptococcus pneumoniae*) and some atypical Pathogens
Third generation	Levofloxacin Sparfloxacin Gatifloxacin Moxifloxacin	Same as for second-generation agents plus expanded gram-positive coverage (penicillin-sensitive and penicillin-resistant *S. pneumoniae*) and expanded activity against atypical Pathogens
Fourth generation	Trovafloxacin	Same as for third-generation agents plus broad anaerobic coverage

Quinolones: Mechanism of Action

- Block the bacterial DNA synthesis by inhibiting of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction.

Clinical Uses

- Urinary tract infection
- Anthrax
- Gonorrhea
- Gastrointestinal tract Infections
- Resistant Respiratory Infections

Adverse Effects

- Gastrointestinal
  Nausea, vomiting and diarrhoea
- Central nervous system problems
  Headache and dizziness or light headedness
- Phototoxicity
- Liver toxicity
  Trovafloxacin is associated with serious liver injury and therefore use of the drug is restricted to infections that re life threatening.
- Connective tissue problems
  Cause articular cartilage erosion (arthropathy) occurs in immature experimental animals so Fluoroquinolones should be avoided in pregnancy, in nursing mothers and in children under eighteen years of age.

Quinolones' Dispensing Issues

- Antacids interfere with absorption
- Avoid exposure to sun