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Topic: Antibiotics

What is an antibiotic?

"Antibiotic" is from antibiosis, meaning against life.

Substances derived from a microorganism or produced synthetically (Sulfonamides & Quinolones) to kill or suppress the growth of other microorganisms.

Classification of Antibiotics

Antibiotics are classified by several ways:

- On the basis of mechanism of action
- On the basis of spectrum of activity
- On the basis of mode of action

Mechanism of action of antimicrobial agents

1. Inhibition of cell wall synthesis:

- Penicillins, Cephalosporins, Bacitracin & Vancomycin

2. Inhibition of functions of cellular membrane:

- Polymyxins

3. Inhibition of protein synthesis:

- Chloramphenicol, Macrolides & Clindamycin
- Tetracyclines & Aminoglycosides

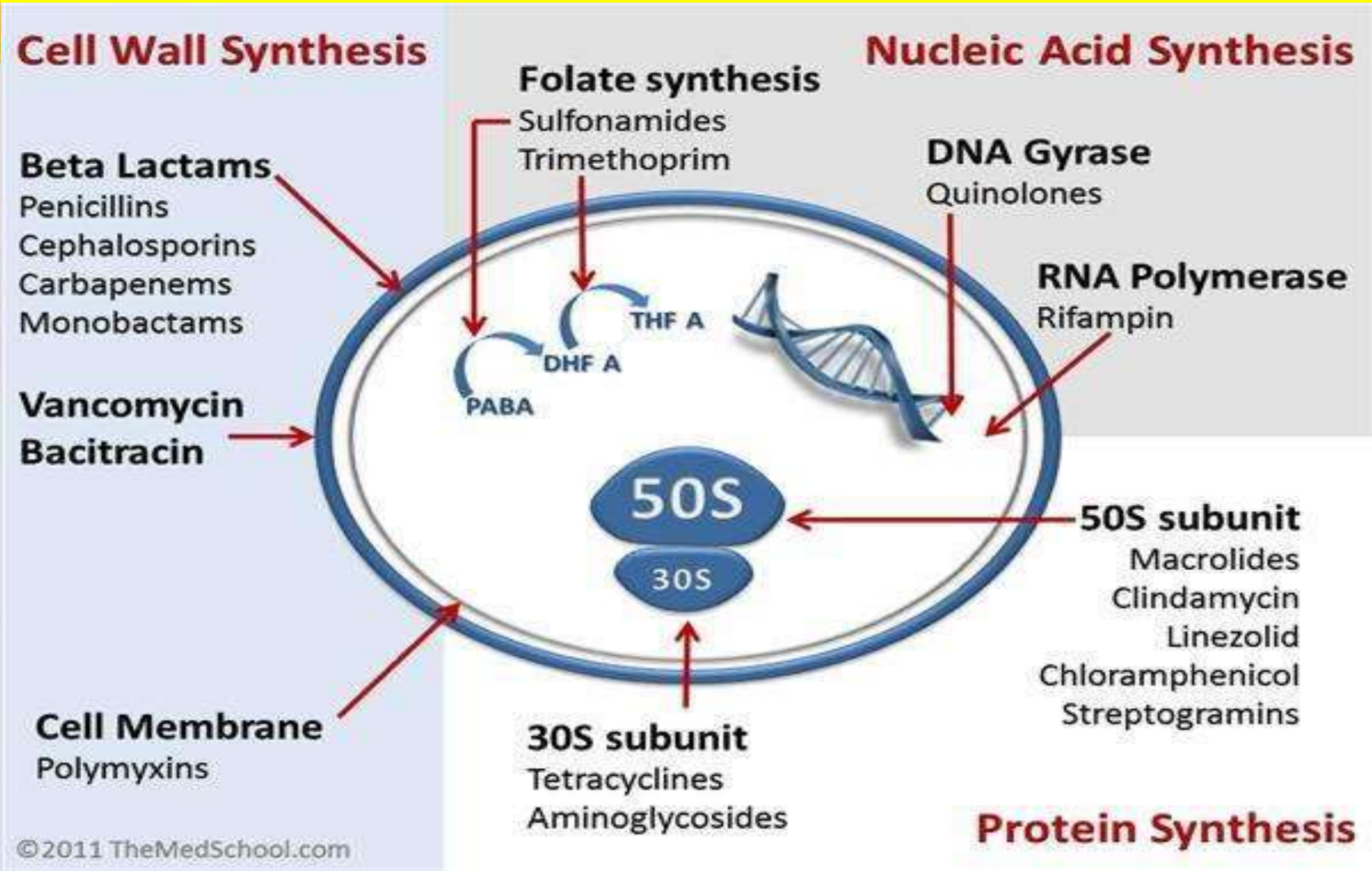
4. Inhibition of nucleic acid synthesis:

- Quinolones
- Rifampin

5. Inhibition of folic acid synthesis:

- Sulfonamides & trimethoprim

On the basis of mechanism of action



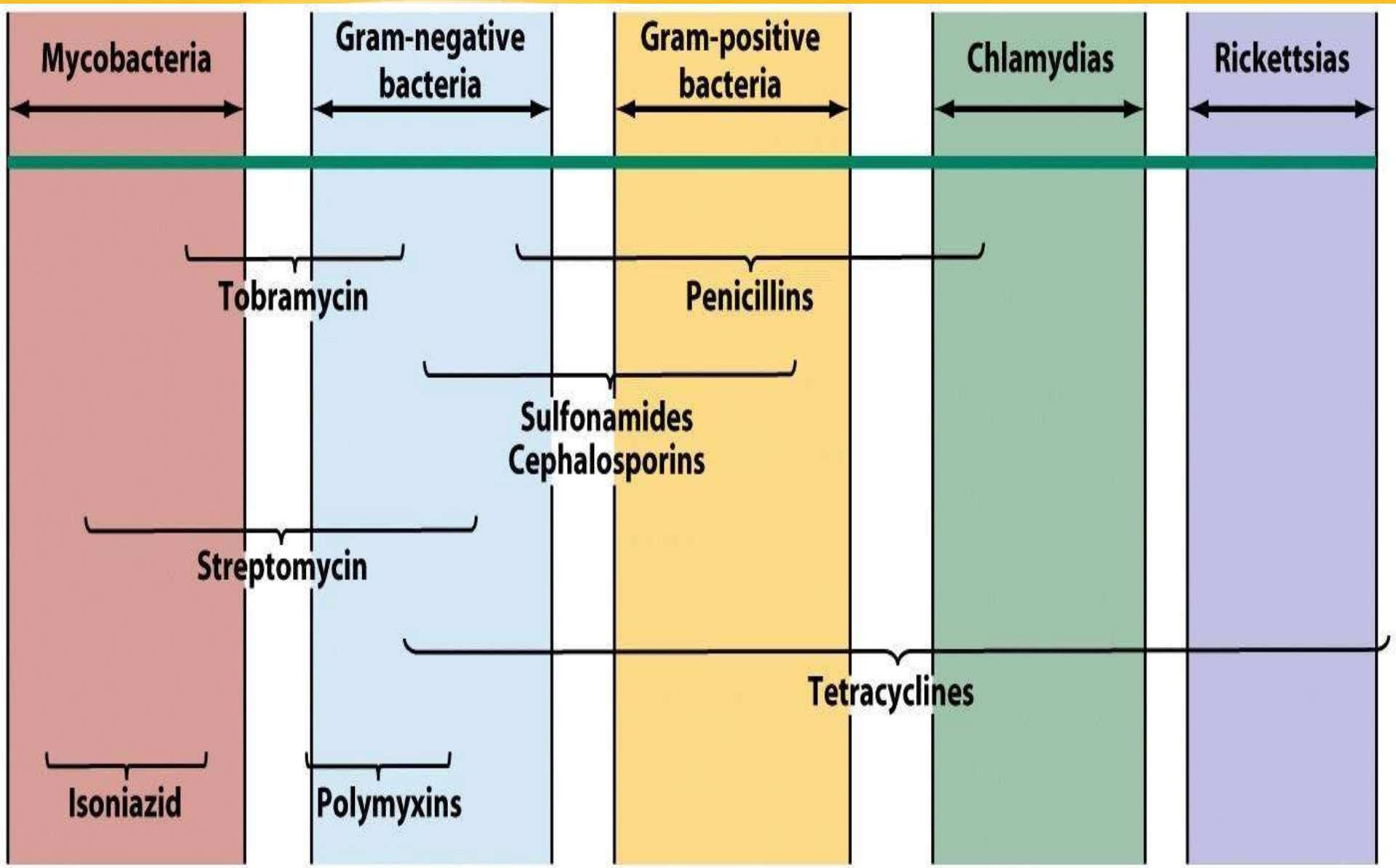
Antimicrobial Spectrum

Antimicrobial spectrum: the scope that a drug kills or suppresses the growth of microorganisms.

Narrow-spectrum: The drugs that only act on one kind or one strain of bacteria.(Isoniazide)

Broad-spectrum: The drugs that have a wide antimicrobial scope.(Tetracycline & Chloramphenicol)

On the basis of spectrum of activity



On the basis of mode of action

Bacteriostatic antibiotics:	• Tetracycline • Chloramphenicol • Erythromycin • Lincomycin
Bacteriocidal antibiotics:	• Cephalosporin • Penicillin • Erythromycin • Aminoglycosides • Cotrimoxazole

Misuse of Antibiotics

Antibiotic misuse, sometimes called antibiotic abuse or antibiotic overuse

The misuse or overuse of antibiotics, may produce serious effects on health.

It is a contributing factor to the creation of multidrug-resistant bacteria, informally called “super bugs”.

Antibiotic Resistances and Cross Resistances

Antibiotic resistance is the phenomenon that susceptibility of pathogenic microorganisms to antibiotic becomes lower or even loses after the microorganisms contact with antibiotic many times.

When the bacteria show resistance to one antibiotic, they are also resistant to some other antibiotics. This phenomenon is called cross antibiotic resistance.

Mechanisms of Antibiotic Resistance

1. Alteration of the target site of the antibiotic

- One of the most problematic antibiotic resistances worldwide, methicillin resistance among Staphylococcus aureus

2. Enzyme inactivation of the antibiotic

- β-lactam antibiotics (Penicillins & Cephalosporins) can be inactivated by β-lactamases.

Mechanisms of Antibiotic Resistance Cont.

3.Active transport of the antibiotic out of the bacterial cell

- Active transport of the antibiotic out of the bacterial cell (efflux pumps) as removal of some antibiotics e.g. Tetracyclines, Macrolides & Quinolones

4.Decreased permeability of the bacterial cell wall to the antibiotic

- Alteration in the porin proteins that form channels in the cell membrane e.g. Resistance of Pseudomonas aeruginosa to a variety of Penicillins & Cephalosporins

Mechanisms of Antibiotic Resistance

Decreased Permeability

β lactams
Amioglycosides

Efflux Pump

Tetracyclines
Quinolones
Macrolides

Altered Target

β lactams
Quinolones
Amioglycosides
Vancomycin
Macrolides
TMP/SMX

Enzymatic Inactivation

General Principles of Antimicrobial Therapy

- Identification of the infecting organism should precede antimicrobial therapy when possible.
- The pathogenic microorganism susceptibility to antimicrobial agents should be determined, if a suitable test exists.
- Factors that influence the choice of an antimicrobial agent or its dosage for a patient include the age, renal & hepatic function, pregnancy status and the site of infection, etc.

Selection of Antimicrobial Agent

- Empiric therapy - prior to identification of Organism - critically ill patients
- Organism's susceptibility to the antibiotic
- Patient factors - immune system, renal/hepatic function
- Effect of site of infection on therapy - blood brain barrier
- Safety of the agent
- Cost of therapy

Ideal Antimicrobial Agent

- Have highly selective toxicity to the pathogenic microorganisms in host body
- Have no or less toxicity to the host
- Low propensity for development of resistance
- Not induce hypersensitive reactions in the host
- Have rapid and extensive tissue distribution
- Be free of interactions with other drugs
- Be relatively inexpensive

Complications of Antibiotic Therapy

- Resistance due to inappropriate use of antibiotics
- Hypersensitivity (Penicillin)
- Direct toxicity (Aminoglycosides = ototoxicity)
- Super infections (broad spectrum antimicrobials cause alteration of the normal flora; often difficult to treat)

Antimicrobial Combination

Results of Combination Therapy:

- Additive (indifferent) effect: the activity of two drugs in combination is equal to the sum (or a partial sum) of their independent activity when studied separately.
- Synergistic effect: the activity of two drugs in combination is greater to the sum of their independent activity when studied separately.
- Antagonistic effect: the activity of two drugs in combination is less to the sum (or a partial sum) of their independent activity when studied separately.

Indications for the Clinical Use of Antimicrobial Combinations

- Prevention of the emergence of resistant organisms
- Polymicrobial infection
- Initial therapy
- Decreased toxicity
- Synergism

Prevention of the Emergence of Resistant Organisms

- Decreased resistant mycobacterium tuberculosis with combination
- Reduction of β-lactamase induction with combination β-lactam agents and Aminoglycosides

Polymicrobial Infection

- Intra-abdominal infection
- Pelvic infection
- Mixed aerobic and anaerobic organism

Initial Therapy

- Neutropenic patients
- In patients where the nature of infection is not clear yet

Decreased Toxicity

- Decrease the toxic drug required for treatment and thus reduce the dose related toxicity

Synergism

Enhanced Uptake of Aminoglycosides when Combined with β-lactam agents

- Treatment of enterococcal endocarditis: ampicillin & gentamicin
- Viridans streptococcal endocarditis: penicillin & gentamicin
- Staphylococcal bacteremia: vancomycin & gentamicin
- Treatment of pseudomonas infections: β-lactam agent & Aminoglycosides

Inhibition of Sequential Steps

- Sulfonamide with trimethoprim
- Treatment and prevention of chronic urinary tract infection, typhoid fever, shigellosis caused by organisms resistant to ampicillin

Inhibition of enzymatic activation

Disadvantages of the Inappropriate Use of Antimicrobial Combination

- Antagonism
- Increased cost
- Adverse effects
- Super infections (alteration of the normal flora; often difficult to treat)

Classes of Antibiotics

The main classes of antibiotics are:

- Beta-Lactams
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
- Macrolides & Ketolides
- Aminoglycosides
- Fluoroquinolones
- Tetracyclines, Amphenicols

Penicillins

- The penicillins are the oldest class of antibiotics. Penicillins have a common chemical structure which they share with the Cephalosporins.
- Penicillins are generally bactericidal, inhibiting formation of the cell wall. Penicillins are used to treat skin infections, dental infections, ear infections, respiratory tract infections, urinary tract infections, gonorrhea.

Types of penicillins

- ***The natural penicillins***

  Penicillin G

- ***Penicillinase-resistant penicillins***

  Methicillin & Oxacillin

- ***Aminopenicillins***

  Ampicillin & Amoxicillin

Penicillins side effects

- Diarrhea, nausea, vomiting, and upset stomach
- In rare cases Penicillins can cause immediate and delayed allergic reactions - specifically skin rashes, fever & anaphylactic shock.
- Penicillins are classed as category B during pregnancy.

Cephalosporins

- Cephalosporins have a mechanism of action identical to that of the Penicillins.
- Interferes with synthesis of the bacterial cell wall and so are bactericidal.

- Cephalosporins are used to treat pneumonia, strept throat, staph infections, tonsillitis, bronchitis, otitis media, various types of skin infections, gonorrhea, urinary tract infections.

- Cephalosporins antibiotics are also commonly used for surgical prophylaxis. Cephalexin can also be used to treat bone infections.

The first generation Cephalosporins

- They possess generally excellent coverage against most Gram-positive pathogens and variable to poor coverage against most Gram-negative pathogens.

- The first generation includes:

  Cephradine (Velosef)

  Cephalexin (Ceporex)

  Cefadroxil (Biodroxil, Duricef)

The second generation Cephalosporins

- In addition to the Gram-positive spectrum of the first generation Cephalosporins, these agents have expanded Gram-negative spectrum.
- Cefoxitin and Cefotetan also have good activity against Bacteroides fragilis.

- The second generation includes:

  Cefaclor (Bacticlor)

  Cefuroxime (Zinnat)

The third generation Cephalosporins

- They have much expanded gram negative activity. However, some members of this group have decreased activity against gram-positive organisms. They have the advantage of convenient administration, but they are expensive.
- The third generation includes:

  Ceftazidime (Fortum) Cefixime

  (Suprax) Cefoperazone

  (Cefobid) Cefotaxime

  (Claforan, Cefotax)

  Ceftriaxone (Ceftriaxone, Rociphen)

  Cefdinir (Omnicef)

The fourth generation Cephalosporins

- They are extended-spectrum agents with similar activity against Gram-positive organisms as first-generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins.
- Many fourth generation cephalosporins can cross blood brain barrier and are effective in meningitis.

- The fourth generation includes:

  Cefepime (Maxipime)

The Fifth generation Cephalosporins

- Used to treat MRSA (methicillin-resistant Staphylococcus aureus), penicillin-resistant Streptococcus pneumoniae, Pseudomonas aeruginosa, and enterococci.

- The fifth generation includes:

  Ceftaroline (Teflaro)

  Ceftobiprole (Zeftera)

Cephalosporins side effects

- Diarrhea, nausea, mild stomach upset
- Approximately 5–10% of patients with allergic hypersensitivity to penicillins will also have cross-reactivity with cephalosporins.
- Cephalosporin antibiotics are classed as pregnancy category B.

Carbapenems

- A class of β-Lactam antibiotics with a broad spectrum of antibacterial activity.
- Highly resistant to most β-lactamases.
- Active against both Gram-positive and Gram-negative bacteria, and anaerobes, with the exception of intracellular bacteria (atypical), such as the *Chlamydia*.

- Agents:

  Imipenem/Cilastatin (Tienem)

  Meropenem (Meronem)

- Adverse effects to Carbapenems include headache, rash, GI upset, phlebitis, hypotension, seizures in patients with renal dysfunction.

Monobactams

- They are β-lactam compounds.
- They work only against aerobic Gram negative bacteria (Neisseria, Pseudomonas).
- The only commercially available Monobactams antibiotic is Aztreonam (Azactam).
- Adverse effects to Monobactams can include skin rash and occasional abnormal liver functions.

Macrolides

- Macrolides are bacteriostatic, binding with bacterial ribosomes to inhibit protein synthesis.
- Macrolides antibiotics are used to treat respiratory tract infections (such as pharyngitis, sinusitis, and bronchitis), genital, gastrointestinal tract & skin infections.

- Macrolides antibiotics are:

  Erythromycin (Erythrocin)

  Clarithromycin (Klacid)

  Azithromycin (Zithromax)

  Roxithromycin (Roxicin)

Macrolides side effects

- Nausea, vomiting, diarrhea; infrequently, there may be temporary auditory impairment.
- Oral Erythromycin may be highly irritating to the stomach and when given by injection may cause severe phlebitis.
- Macrolides antibiotics should be used with caution in patients with liver dysfunction.
- Pregnancy category B: Azithromycin, Erythromycin.
  Pregnancy category C: Clarithromycin

Ketolides

- Antibiotics belonging to the Macrolides group.
- Much broad spectrum than other Macrolides.
- Ketolides are effective against Macrolides-resistant bacteria, due to their ability to bind at two sites at the bacterial ribosome as well as having a structural modification that makes them poor substrates for efflux-pump mediated resistance.
- The only Ketolide on the market at this moment is telithromycin, which is sold under the brand name of Ketek.

Lincosamides (e.g. lincomycin, clindamycin)

- Lincosamides prevent bacteria replicating by interfering with the synthesis of proteins.

- They are normally used to treat staphylococci and streptococci, and have proved useful in treating Bacteroides fragilis and some other anaerobes.

- They are used in the treatment of Toxic Shock Syndrome.

- Lincosamides antibiotics are one of the classes of antibiotics most associated with pseudomembranous colitis caused by C. difficile.

Aminoglycosides

- The Aminoglycosides are bactericidal and work by stopping bacteria from making proteins.
- Aminoglycosides antibiotics are used to treat infections caused by Gram-negative bacteria.
- Aminoglycosides may be used along with penicillins or cephalosporins to give a two-pronged attack on the bacteria.
- Since Aminoglycosides are broken down easily in the stomach, they can't be given by mouth and must be injected.

- Generally, Aminoglycosides are given for short time periods.

- Aminoglycosides group includes:

  Amikacin (Amikin)

  Gentamicin (Garamycin)

  Neomycin (Neomycin)

  Streptomycin (Streptomycin)

  Tobramycin (Nebcin)

Aminoglycosides side effects

- Ototoxicity
- Nephrotoxicity
- Aminoglycosides are classed as pregnancy category D.

Fluoroquinolones

- They are synthetic antibiotics, not derived from bacteria.
- Fluoroquinolones are broad-spectrum bactericidal drugs that are chemically unrelated to the penicillins or the cephalosporins.
- Fluoroquinolones inhibit bacteria by interfering with their ability to make DNA. This effect is bactericidal.
- Because of their excellent absorption Fluoroquinolones can be administered not only by intravenous but orally as well.

- Fluoroquinolones are used to treat most common urinary tract infections, skin infections, and respiratory infections (such as sinusitis, pneumonia, bronchitis).

- Fluoroquinolones group includes:

  Ciprofloxacin (Ciprobay, Ciprocin)

  Levofloxacin (Tavanic, Alfacef)

  Norfloxacin (Noracin)

  Ofloxacin (Tarivid)

  Moxifloxacin (Avalox)

Fluoroquinolones side effects

- Nausea, vomiting, diarrhea, abdominal pain
- Irreversible damage to central nervous system (uncommon)
- Tendinosis (rare)
- Fluoroquinolones are classed as pregnancy category C.

Trimethoprim/sulfamethoxazole or Co-trimoxazole

- An antibiotic used in the treatment of a variety of bacterial, fungal and protozoal infections.
- Co-trimoxazole is generally considered bactericidal, although its components are individually bacteriostatic.
- Its actions are antifolate in nature, inhibiting both *de novo* folate biosynthesis and metabolism.

Co-trimoxazole side effects

- Nausea, vomiting
- An allergic reaction and infection with Clostridium difficile, a type of diarrhea
- Co-trimoxazole is classed as pregnancy category C.
- Some state it should not be used during breastfeeding while others say it is okay.

Tetracyclines

- Broad-spectrum bacteriostatic agents and work by inhibiting the bacterial protein synthesis.
- Tetracyclines may be effective against a wide variety of microorganisms, including Rickettsia and Amoebic parasites.
- Tetracyclines are used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, skin, intestines.

- Tetracyclines also are used to treat Gonorrhea, Rocky Mountain spotted fever, Lyme Disease, Typhus.
- Their most common current use is in the treatment of moderately severe acne and rosacea.
- Tetracycline antibiotics are:

  Tetracycline

  Doxycycline (Vibramycin)

  Minocycline

  Oxytetracycline (Oxytetracid)

Tetracyclines side effects

- Cramps or burning of the stomach, diarrhea, sore mouth or tongue
- Skin photosensitivity
- Allergic reactions
- Tetracycline antibiotics should not be used in children under the age of 8 and specifically during periods of tooth development.
- Tetracyclines are classed as pregnancy category D. Use during pregnancy may cause alterations in bone development.

Chloramphenicol

- It is a bacteriostatic.
- It is considered a prototypical broad-spectrum antibiotic, alongside the tetracyclines, and as it is both cheap and easy to manufacture, it is frequently an antibiotic of choice in the developing world.
- Effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms.

- Due to resistance and safety concerns, it is no longer a first-line agent for any infection in developed nations, with the notable exception of topical treatment of bacterial conjunctivitis.

Chloramphenicol side effects

- The most serious adverse effect associated with chloramphenicol treatment is bone marrow toxicity.
- Use of intravenous chloramphenicol has also been associated with gray baby syndrome.
- Other less serious reactions include fever, rashes, headache, confusion.

Glycopeptides (e.g. vancomycin, teicoplanin)

- These antibiotics are effective principally against Gram-positive cocci.
- This class of drugs inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis.
- Vancomycin is used if infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected.

- Due to their toxicity, use of glycopeptides antibiotics is restricted to patients who are critically ill, who have a demonstrated hypersensitivity to the β-lactams, or who are infected with β-lactam-resistant species.

- They exhibit a narrow spectrum of action, and are bactericidal only against the enterococci.

- Oral preparations of vancomycin are available, however they are not absorbed from the lumen of the gut, formulated for the treatment of infections within the gastrointestinal tract, Clostridium difficile, for example.

Vancomycin side effects

- Vancomycin is usually given intravenously, as an infusion, and can cause tissue necrosis and phlebitis at the injection site.
- Red man syndrome, an idiosyncratic reaction to bolus dose caused by histamine release
- Nephrotoxicity including renal failure and interstitial nephritis
- Blood disorders including neutropenia, and deafness, which is reversible once therapy has stopped
- Risk of accumulation in patients with renal impairment

Streptogramins

- Effective in the treatment of vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE), two of the most rapidly growing strains of multidrug-resistant bacteria.

- Members include:

  Quinupristin/dalfopristin

  Pristinamycin

  Virginiamycin

Adverse effects include:

Related to administration via peripheral vein

Inflammation, pain, edema, infusion site reaction, thrombophlebitis

Non-venous adverse effects

- Nausea, vomiting, diarrhea
- Rash
- Headache
- Pain, ill-defined focal or generalized discomfort
- Pruritus
- Arthralgia, myalgia
- Asthenia
- Conjugated hyperbilirubinaemia

Oxazolidinones (e.g. linezolid)

- Linezolid inhibits ribosomal protein synthesis by inhibiting formation of the initiation complex.

- It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.

- Linezolid is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).

- The main indications of linezolid are infections of the skin & soft tissues and pneumonia (particularly hospital-acquired pneumonia).
- Common adverse effects of short-term use include headache, diarrhea & nausea. Long-term use, however, has been associated with serious adverse effects; linezolid can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks. If used for longer periods still, it may cause sometimes irreversible chemotherapy-induced peripheral neuropathy and optic nerve damage, and lactic acidosis.

Ansamycins

- A family of secondary metabolites that show antimicrobial activity against many Gram-positive and some Gram-negative bacteria and includes various compounds, among which: streptovaricins and rifamycins.

- Rifamycins are a subclass of ansamycins with high potency against mycobacteria. This resulted in their widespread use in the treatment of tuberculosis, leprosy, and AIDS-related mycobacterial infections.

- The antibacterial activity of rifamycins relies on the inhibition of bacterial DNA-dependent RNA synthesis. This is due to the high affinity of rifamycins for the prokaryotic RNA polymerase.

Adverse effects include:

- Hepatotoxic - hepatitis, liver failure in severe cases
- Respiratory - breathlessness
- Cutaneous - flushing, pruritus, rash, redness and watering of eyes
- Abdominal - nausea, vomiting, abdominal cramps with or without diarrhea
- Flu-like symptoms - with chills, fever, headache, arthralgia, and malaise, rifampin has good penetration into the brain, and this may directly explain some malaise and dysphoria in a minority of users.

Rifaximin is a semisynthetic antibiotic based on rifamycin. It has poor oral bioavailability, meaning that very little of the drug will be absorbed into the blood stream when it is taken orally. Rifaximin is used in the treatment of traveler's diarrhea and hepatic encephalopathy, for which it received orphan drug status* from the U.S. Food and Drug Administration in 1998.

Rifaximin interferes with transcription by binding to the β-subunit of bacterial RNA polymerase.

* An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition.

Metronidazole

- A nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa.

- It is antibacterial against anaerobic organisms, an amoebicide and an antiprotozoal.

- It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells. This function only occurs when Metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria.

- Metronidazole is primarily used to treat: bacterial vaginosis, pelvic inflammatory disease (along with other antibacterials like ceftriaxone), pseudomembranous colitis, aspiration pneumonia, rosacea (topical), fungating wounds (topical), intra-abdominal infections, lung abscess, gingivitis, amoebiasis, giardiasis, trichomoniasis, and infections caused by susceptible anaerobic organisms such as *Bacteroides.*

- It is also often used to eradicate *Helicobacter pylori* along with other drugs and to prevent infection in people recovering from surgery.

- Adverse effects include:

  Discolored urine, headache, metallic taste , nausea

  Metronidazole is classed as pregnancy category B.


Thank You