Antimicrobial Therapy

Jacquelyn G. Black, Microbiology, 9th Edition

Chapter 13 – Page 371

Mahmoud Alkawareek, PhD

Introduction

- **Chemotherapeutic agent** (drug): any chemical substance used in medical practice
- **Antimicrobial chemotherapy**: the utilization of chemical substances to treat microbial infections
- **Antibiotic**: chemical substances produced by microorganisms that inhibit the growth or destroy other microorganisms when used at low concentration
- Although the definition of antibiotic indicates natural substances, many antimicrobial compounds that are **semisynthetic** (e.g. some β-lactams) or **synthetic** (e.g. sulfonamides & quinolones) are still called antibiotics in common practice

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Properties of Ideal Antimicrobial Agents

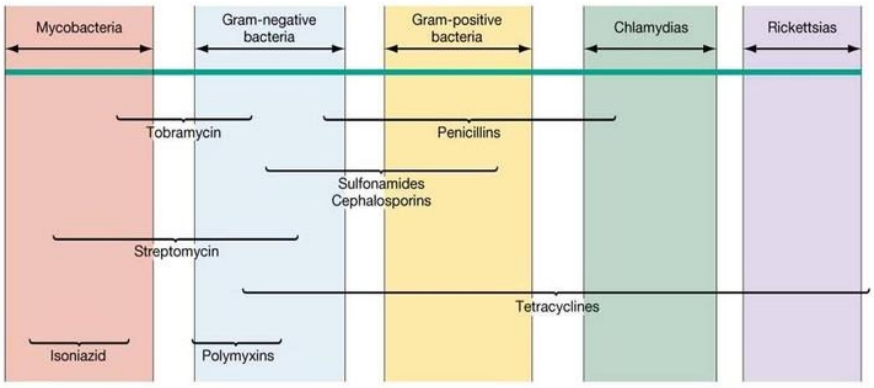
1. **Selective toxicity**:
   - The drug should harm the microbe without significant harm on the host. This means the toxic dosage level (the dose that causes damage to the host) should be much higher than the effective therapeutic dosage level (the dose needed to destroy the microbe).
   - To evaluate toxicity of the drug, **chemotherapeutic index** is used: the ratio between toxic dose & effective dose
2. **Soluble** in body fluids in order to penetrate body tissues
3. Preferably **withstand acidic environment** of the stomach so they can be administered orally

Properties of Ideal Antimicrobial Agents

4. Should not be eliminated (metabolized or excreted) so quickly so that they have time to exert their effect, i.e. should have a relatively **long half life**
5. **Long shelf life** with convenient storage conditions requirement
6. **Low cost**
7. **Minimal side effects** (including allergy)
8. Has no significant effect on **normal microflora**
9. **Resistance** to it not easily acquired by microbes

Spectrum of Antibiotics

- **Broad spectrum antibiotic**: effective against a wide range of microorganisms of different taxonomic groups including G+ve & G-ve bacteria, e.g. tetracycline
- **Narrow spectrum antibiotic**: effective against a small number of microorganisms or single group, e.g. Penicillin G and isoniazid
- If the microorganism is identified, use narrow spectrum AB, because narrow spectrum reduce the possibility of producing resistance in microorganisms, also using broad spectrum will destroy the normal flora
  - Normal flora indicates the indigenous microbes that live in/on the host & prevent the growth of pathogenic microbes
- If the patient is seriously ill & the microbe is not identified, broad spectrum AB is useful in this case.

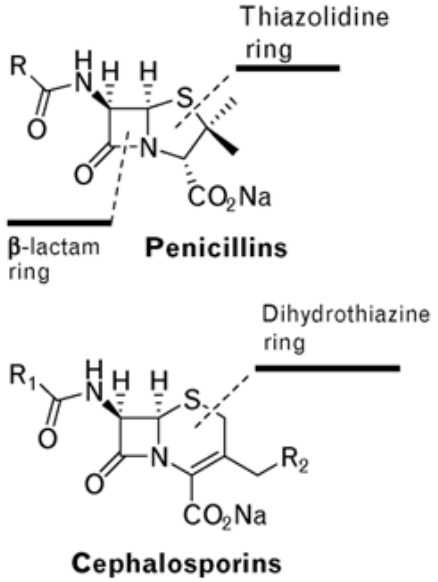


Antibiotics Modes of Action

- Antibiotics can have **bactericidal** effect (killing effect) or **bacteriostatic** effect (inhibit bacterial growth)
  - In case of bacteriostatic agents, the host immune system is supposed to destroy & eliminate the microbe
- There are 5 major modes of action through which antibiotics act on microbes:
  1. Inhibition of cell wall synthesis
  2. Inhibition of protein synthesis
  3. Disruption of cell membrane
  4. Inhibition of nucleic acid synthesis
  5. Action as antimetabolites

Cell Wall Inhibitors

- Most bacteria have external rigid cell walls, while human cells don't
  - Therefore antibiotics that **disrupt cell wall synthesis** will cause the bacterial cells (but not human cells) to **burst** when present in low osmotic pressure in body fluids
- The main group of AB that act on bacterial cell wall is the '**beta lactams'**; so called due to presence of a β-lactam ring.
- Beta lactam antibiotics include **penicillins**, **cephalosporins** & some **other agents** (carbapenems & monobactams)



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β-Lactams Mode of action

- β-Lactam antibiotics are **bactericidal agents** that act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls
- β-lactams are analogues to D-alanyl-D-alanine residue of the peptidoglycan chain which is the substrate for the **transpeptidase enzymes** (these enzymes are called penicillin-binding proteins-PBPs)
- As such, they bind irreversibly to transpeptidase & inhibit it from cross linking the peptidoglycan chains, so the cell wall continues to form but become weaker which causes the cell to swell & lyse in hypoosmotic fluids

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Penicillins

- The first naturally isolated AB was **benzylpenicillin (penicillin-G)**:
  - Isolated from mold *Penicillium notatum*.
  - It is administered parenterally because it is degraded by stomach acids.
    - Potassium salt of benzylpenicillin is used IV
    - Procaine or benzathine salts of benzylpenicillin are used IM (prolonged action)
  - It is effective against G+ve bacteria (narrow spectrum) because it is unable to penetrate G-ve cell wall
- **Penicillin-V** is naturally occurring, similar to Penicillin-G, but is less acid labile i.e. can be taken orally

Penicillins

- **Semisynthetic penicillins**: they have the same nucleus of natural penicillin but with side chains added chemically
  - **Ampicillin** and **Amoxicillin**: acid stable (given orally) with broader spectrum of activity than Penicillin-G, i.e. act on both G+vd and G-ve bacteria.
  - **Carbenicillin, ticarcillin** and **piperacillin**: broad spectrum (also called extended-spectrum penicillins); especially useful against ***Pseuodomonas* infections**, but used parenterally.

Penicillins

- A problem that faces penicillins is that they are degraded by naturally occurring bacterial **β-lactamase enzyme** (a group of it called penicillinase); which breaks b-lactam ring & inactivate the drug
- However, there are some penicillins which are intrinsically resistant to β-lactamases such as:
  - **Methicillin**: semisynthetic, narrow spectrum (G+ve), used for bacteria that are resistant to penicillin.
    - In the past Methicillin was the ultimate solution for treating resistant bacteria mainly *Staphylococcus aureus*, until 'methicillin resistant *Staphylococcus aureus*' has emerged (MRSA)
  - Other lactamase-resistant penicillins, similar to methicillin, are also available including **oxacillin**, **cloxacillin** and **nafcillin**
    - These are also semisynthetic agents with narrow spectrum of activity (G+ve) used primarily for lactamase-producing *Staphylococcus aureus*

Penicillins

- Another approach used to overcome the degradation of penicillin drugs by β-lactamase enzyme is to administer them in combination with **β-lactamase inhibitors**, such as **clavulanic acid** (used with amoxicillin) and **tazobactam** (used with piperacillin)
- Penicillins generally are **nontoxic**, but 1-5% of adults are **allergic** to them (penicillin allergy is rare among children), in extreme cases death may result from the anaphylactic shock associated with such allergy!
- Penicillins may be used **prophylactically** (to prevent infections) before surgeries

Cephalosporins

- Naturally occurring ones (e.g. Cephalosporin C), produced from fungus *Cephalosporium (Acremonium)*, have little antimicrobial activity
  - Thus most cephalosporins currently used are **semisynthetic** derivatives
- Cephalosporins generally have broader spectrum than penicillins & are more resistant to β-lactamases. But still are degraded by cephalosporinase enzymes (a group of β-lactamases)
- Semisynthetic cephalosporins differ by their side chains. They are divided into generations (1st, 2nd, 3rd, 4th and 5th generation)
  - When resistance appeared to old generations new generation was produced
  - The aim of these generations was to broaden spectrum of activity & increase resistance to β-lactamases

Cephalosporins

- 1st generation: better activity against G+ve bacteria, few G-ve
- 2nd generation: more active on G-ve, some G+ve, more resistant to β-lactamases
- 3rd generation: (with some exceptions) more G-ve activity, few G+ve
- 4th generation: have both G+ve & G-ve activity (used for hospital acquired infections)
- 5th generation have very good activity against both G+ve & G-ve (particularly useful against MRSA),

Generation	Agents	Route of Administration	Spectrum/Main Indications
First	Cephalexin	Oral	G+ve/ limited G-ve
	Cefradine		G+ve
	Cefadroxil	Oral/Parenteral	G+ve/ limited G-ve
	Cefazolin	Parenteral	G+ve cocci
	Cephalothin		G+ve cocci
Second	Cefaclor	Oral	G+ve (less than 1st generation) and G-ve
	Cefprozil		
	Cefuroxime	Oral/Parenteral	
	Cefoxitin	Parenteral	
Third	Cefixime	Oral	Broad Spectrum
	Cefpodoxime		
	Ceftriaxone	Parenteral	V. good G-ve (excluding *Pseudomonas*), some G+ve
	Cefotaxime		
	Ceftazidime		Mainly G-ve (including *Pseudomonas*)
Forth	Cefepime	Parenteral	Extended spectrum (inc. *Pseudomonas*)
Fifth	Ceftaroline	Parenteral	Broad Spectrum (inc. MRSA)
	Ceftobiprole		Exd. spectrum (inc. *Pseudomonas* &MRSA)

Cephalosporins

- Cephalosporins can be used with some patients that are allergic to penicillins, but since cephalosporins are structurally similar to penicillins, 4-15% of patients who are allergic to penicillins are also allergic to cephalosporins
- Penicillins & cephalosporins exert their activity against metabolically active bacteria; so they are not supposed to be used with bacteriostatic agents

Monobactams

- The β-lactam ring is alone and not fused with another ring
- **Aztreonam** is an example drug of this group
- Effective only against G-ve bacteria, including *Pseudomonas aeruginosa*
- Used for meningitis, UTI & kidney infections
- No cross allergy with penicillins has been observed
- Usually resistant to β-lactamases
- Administered only parenterally

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Carbapenems

- A group of β-lactams that are highly resistant to β -lactamases
- e.g. **imipenem** and **meropenem**
- Active against G+ve & G-ve bacteria including *Pseudomonas aerogenosa* & *Enterococcus*
- Imipenem is usually coadministered with **cilastatin**, a compound which inhibits imipinem degradation in kidneys (not needed with meropenem)
- Administered only parenterally

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Vancomycin

- A large complex **glycopeptide** produced by soil bacteria **actinomycetes**
- Its large size prevents its penetration through G-ve pores in the outer membrane, therefore it is not effective against most G-ve bacteria (i.e. **effective mainly against G+ve bacteria**)
- It acts by binding to the D-alanyl-D-alanine residue & forming a complex with it which inhibits peptidoglycan synthesis
- Administered **parenterally** (in hospitals since it needs continuous monitoring)

Vancomycin

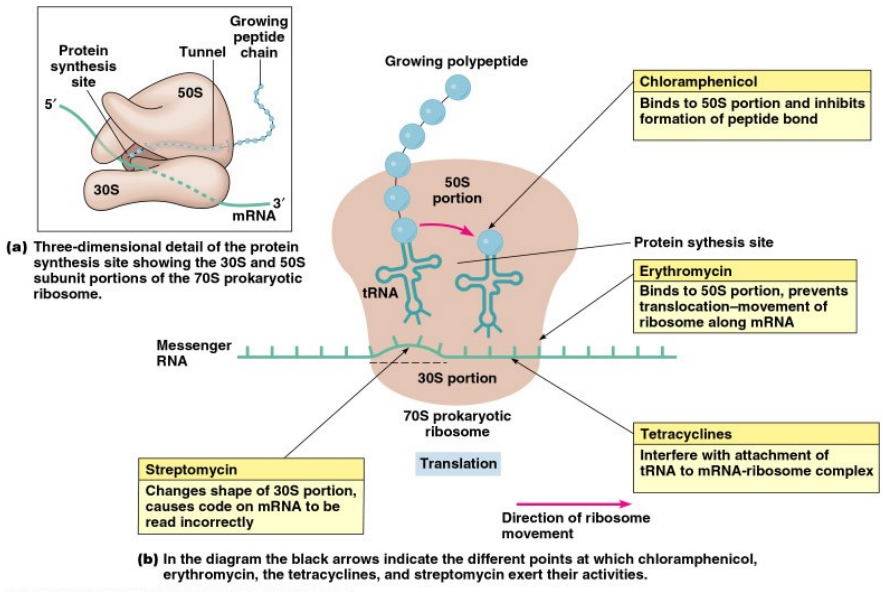
- Due to its high toxicity (nephrotoxicity and ototoxicity), it is only used as a **last resort** for bacteria that are resistant to methicillin & cephalosporins (e.g. MRSA & *Enterococci*)
  - Vancomycin's toxicity is further exacerbated when used in combination with aminoglycosides
- It is also the drug of choice for treating **pseudomembranous colitis**
  - enteritis with formation of false membranes on stool
  - an infection (superinfection) by *Clostridium difficile* that results from the use of broad spectrum antibiotics
- It was used for 40yrs without having resistance against it until strains of **vancomycin resistant *Staphylococcus aureus*** (VRSA) have emerged

Bacitracin

- A mixture of cyclic **polypeptides** produced by ***Bacillus*** bacteria with **bactericidal** activity
- It inhibits cell wall synthesis by interfering with the molecules that carry peptidoglycan subunits across cell membrane to their site in the cell wall
- It is highly effective against **G+ve bacteria**
- It has high toxicity (nephrotoxic), therefore it is usually used topically (i.e. skin and mucus membranes)

Protein Synthesis Inhibitors

- These drugs act on bacterial (70S) ribosomes
  - Since bacterial ribosomes (30S+50S=70S) are different from animal ribosomes (60S+40S=80S), these antibiotics have good **selectivity**
- They include aminoglycosides, tetracyclines, macrolides, lincosamides, streptogramins and oxazolidinones
- They are **bacteriostatic** agents except aminoglycosides which are bactericidal at high concentrations



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome.

(b) In the diagram the black arrows indicate the different points at which chloramphenicol, erythromycin, the tetracyclines, and streptomycin exert their activities.

Aminoglycosides

- Obtained from different species of *Streptomyces* & *Micromonospora*
- They bind to **30S subunit** and cause **misreading of mRNA** resulting in altered amino acid composition and/or premature termination
- They are active against G-ve bacteria including (*Pseudomonas* & *Enterobacter*), some G+ve bacteria and Mycobacteria
- Aminoglycosides act **synergistically** with other drugs (e.g. cephalosporins & penicillins); therefore, in most cases, they are used in combination with other drugs

Aminoglycosides

- They have varying degree of **nephrotoxicity** (damage kidney cells causing protein excretion) & **ototoxicity** (damaging 8th cranial nerve)
- Due to their toxicity, they are used in treating **complicated infections** (e.g. complicated urinary tract infections, peritonitis, joint & bone infections) or to treat **bacteria resistant to other drugs**
- They are not absorbed in GIT and hence administered parenterally or topically

Aminoglycosides

- Aminoglycosides include:
  - Streptomycin (usually used in combination with other drugs to treat TB & plague)
  - Gentamicin
  - Tobramycin
  - Neomycin
  - Kanamycin
  - Netilmicin
  - Amikacin

Tetracyclines

- Produced from ***Streptomyces*** species and some are semisynthetic derivatives
- They bind to **30S subunit** preventing the attachment of tRNA to the mRNA-ribosome complex
- They are absorbed from the GIT and hence can be administered **orally**
- Tetracyclines form complexes with **calcium** & become inactive, therefore milk & dairy products should not be taken with them.
  - Due to their binding with calcium, they also cause **teeth discoloration** & **abnormal bone formation** so they are usually contraindicated during the second half of pregnancy or for children under the age of 5

Tetracyclines

- They have the **widest spectrum of activity** (G+ve, G-ve & mycoplasma)
  - They also can enter the host cells, therefore useful for intracellular infections (i.e. *Rickettsia* & *Chlamydia*)
  - Because of their wide spectrum, they **destroy the intestinal normal flora** resulting in severe GIT disorders and superinfections by *Staphylococcus*, *Pseudomonas*, *Clostridium* and yeasts
- Tetracyclines include:
  - Tetracycline
  - Chlortetracycline
  - Minocycline
  - Doxycycline

Tigecycline

- It was approved by the FDA in 2005
- It belongs to a new class of antibiotics called glycylcycline which is structurally similar to tetracyclines (a derivative of minocycline)
- It has a mechanism of action similar to that of tetracyclines (i.e. binds to 30S subunit …)
- Has broad spectrum of activity (excluding *Pseudomonas*)
- Mainly used against MRSA
- Administered only parenterally

Chloramphenicol

- It is a **bacteriostatic** agent originally derived from ***Streptomyces*** bacteria, but nowadays it can be produced **synthetically**
- It acts on **50S subunit** in a way to prevent peptide chain elongation
- It has a **broad spectrum** of activity (excluding *Pseudomonas* & *Enterococcus*)
- But it has serious side effects such as **aplastic anemia** and **bone marrow suppression** which could be fatal
  - Therefore, its use is considered as a **last choice** when other effective agents are unavailable
  - Among its main uses is to treat **typhoid fever** & **meningitis** for patients who are allergic to cephalosporins & penicillins

Macrolides

- A group of compounds which have a macrolide ring
- They are **bacteriostatic** agents
- Acts on **50S** ribosomal subunit in a way to prevent peptide chain elongation
- They are readily absorbed through the GIT and hence can be administered orally
- They are active against most G+ve bacteria: *Streptococci*, *Pneumococci*, *Staphylococci*, *Corynebacteria* & also *Mycoplasma*.
- Macrolides have variable activity against G-ve bacteria

Macrolides

- Macrolides main use is for penicillin resistant infections & as alternative to penicillin for patients allergic to them.
- Very important for treating **Legionnaires' disease** (pneumonia like disease) caused by *Legionella pneumophila*
- Macrolides include:
  - **Erythromycin**: one of the safest commonly used drugs
  - **Roxithromycin**
  - **Azithromycin**
  - **Clarithromycin**: a member of the triple therapy used to treat *Helicobacter pylori* responsible for stomach & duodenal ulcers

Lincosamides

- Bacteriostatic agents that bind to **50S** subunit & inhibit polypeptide elongation and cause early release of the polypeptide chain
- Include **clindamycin** & **lincomycin**.
  - Clindamycin is less toxic than lincomycin
- Clindamycin is used to treat *Bacteroids* & other **anaerobic bacteria**
  - But it is not effective against *Clostridium defficile*
- Also used for G+ve cocci (except *Enterococci*) and in topical preparations for **acne**
- Clindamycin also has antiprotozoan activity (i.e. used for malaria and toxoplasmosis)
- Long term use of clindamycin causes **pseudomembranous colitis** due to toxins from *Clostridium difficile*

Streptogramins

- Relatively new drugs that comprise a group of macromolecules produced by *Streptomyces* ,
- Includes **streptogramin A & B** and their derivatives
- A combination of 70% **dalfopristin** and 30% **quinopristin** (which are derivatives of streptogramin A & Streptogramin B, respectively) are usually used.
- Both interact with the ribosome at different sites & act synergistically to inhibit protein synthesis.
  - Dalfopristin inhibits early stages of protein synthesis while quinopristin prevents polypeptide elongation & causes early release of the polypeptide chain

Streptogramins

- Administered parentrally
- They are effective against **G+ve bacteria** resistant to other antibiotics including vancomycin
- Used for **life threatening infections** caused by vancomycin resistant *Enterococcus faecium* (G+ve bacteria that cause skin, blood & abdominal infections), MRSA and *Streptococcus pyogenes*

Oxazolidinone

- A new class of antibiotics which includes **linezolid**
- Unlike most other protein synthesis inhibitors, it inhibits the **initiation** of protein synthesis
  - i.e. it prevents the formation of ribosome-mRNA-tRNA complex
- It is mainly used to treat complicated infections caused by multidrug-resistant **G+ve bacteria** such as MRSA, VRSA and VRE (vancomycin-resistant enterococci)
- It can be administered orally, but it is highly expensive

Disrupters of Cell Membrane

- Animal cells have cell membranes that differs than bacterial or fungal membranes, this allows for selective action of antibiotics
- Includes polyenes and cyclic lipopeptides
- **Polyenes**:
  - Such as the antifungal agents **amphotericin B** & **nystatin**
  - They bind to certain sterols (ergosterol) present in the fungal membrane forming transmembrane holes which results in leakage of the intracellular components
  - But they have low therapeutic index

Cyclic Lipopeptides

- Includes polymyxins and daptomycin
- **Polymyxins:**
  - There are different compounds designated as A, B, C, D, E
  - Act as detergents which bind to the phospholipids and **disrupts the membrane permeability** causing leakage of the intracellular components and membrane depolarization
  - Cause serious side effects if taken systemically (parenterally) thus need continuous monitoring
  - Generally, they are used **topically** for skin infections caused by **G-ve bacteria** like *Pseudomonas*, and also in wounds & burns

Cyclic Lipopeptides

- **Daptomycin:**
  - It inserts into the cell membrane forming aggregates which results in membrane disruption and depolarization
  - Active against **G+ve bacteria** (including multidrug-resistant strains such as VRE and MRSA)
  - It is administered parenterally but can induce serious side effects

Inhibitors of Nucleic Acid Synthesis - Quinolones

- Quinolones are a group of synthetic antibiotics that act by inhibiting **DNA gyrase** (the enzyme which unwinds DNA double helix preparing it to replication) thus inhibiting DNA synthesis
- The basic drug of this group is **nalidixic acid**, but the majority of drugs in clinical use belong to the subgroup **fluoroquinolones** such as **ciprofloxacin, norfloxacin, enoxacin** and **ofloxacin**
- They are active against **both G+ve & G-ve** bacteria (including ***Pseudomonas aeruginosa***)
- Used mainly for traveler's diarrhea & urinary tract infections caused by bacteria that are resistant to other antibiotics
- **Levofloxacin**: is a newer generation drug used mainly for community acquired pneumonia, sinusitis and acute exacerbations of chronic bronchitis

Inhibitors of Nucleic Acid Synthesis - Rifamycins

- It includes **rifampin/rifampicin** which is a semisynthetic drug that binds to **RNA polymerase** & blocks mRNA synthesis
- It penetrates tissues therefore used against **Mycobacteria** to treat TB as part of the cocktail treatment
- It **stimulates liver enzymes** that metabolize other drugs (such as oral contraceptives and anticoagulants) reducing their activity
- At high doses it turns the skin and body secretions like tears, sweat, saliva, breast milk & urine to **orange-red color**
- At high doses, it also can result in liver damage

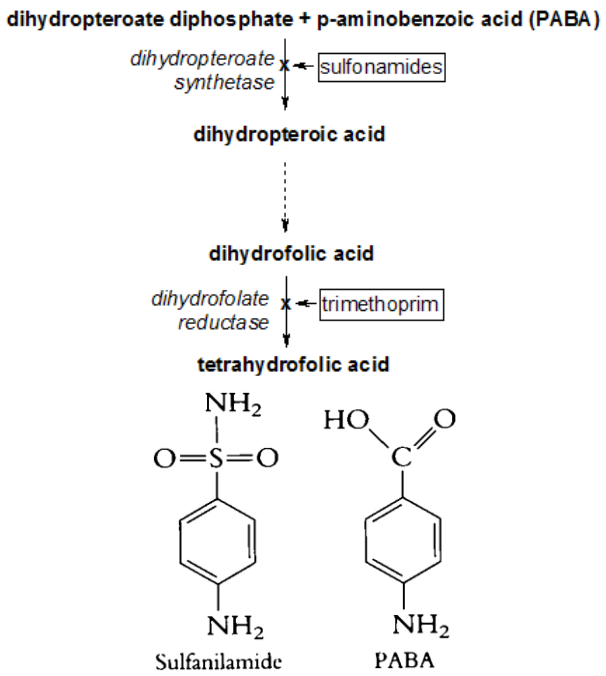
Antimetabolites

- A group of compounds that are structurally similar to normal microbial metabolites, therefore they interfere with microbial metabolic reactions.
- They act by 2 ways
  - Competitive inhibition to the enzyme:

    They resemble the substrate of a metabolic enzyme, thus they bind to the active site of the enzyme & prevent the substrate of the enzyme from binding, this slows or ceases the metabolic reaction.
  - By being **incorporated** into important molecules such as nucleic acids thus inhibiting their function
- Antimetabolites include:
  - Antifolates (sulfa drugs & trimethoprim)
  - Purines analogues
  - Pyrimidines analogues

Sulfonamides (Sulfa Drugs)

- A group of **synthetic** compounds that are **bacteriostatic**
- The first one known was **sulfanilamide**
- They act by competitive inhibition to the enzyme that acts on **para amino benzoic acid (PABA)** needed for folic acid synthesis
  - Folic acid is important for synthesizing nucleic acids & other metabolic products.
  - Sulfonamides are chemically similar to PABA
  - When sulfonamides rather than PABA bind to the enzyme, the bacterium can not make folic acid
  - Animal cells do not produce folic acid & obtain it from diet, on the other hand, bacteria can not use folic acid from diet & should synthesize it, thus sulfonamides are selective in activity



Sulfonamides (Sulfa Drugs)

- They can be used to treat some kinds of **meningitis** as they easily pass the BBB and reach the cerebrospinal fluid
- Example drugs are **sulfadiazine** and **sulfamethoxazole**
- Sulfamethoxazole is usually given **in combination with trimethoprim** which inhibits another enzyme in the pathway of folic acid synthesis
  - This combination drug is called **co-trimoxazole** (abbreviated TMP-SMX or TMP-SMZ)
  - Trimethoprim-sulfonamides are **broad spectrum** and effective against most G-ve & and G+ve bacteria (incl. skin *Staphylococci*)
  - Used for **urinary tract infections** & considered drug of choice for ***Pnemocystis pneumonia*** (fungal complication of AIDS patients)
  - But both drugs are toxic to the **bone marrow** and can induce **hypersensitivity** reactions and **Stevens–Johnson syndrome**

Isoniazid

- Isoniazid is also called isonicotinyl hydrazine (INH)
- It is an **antimetabolite for two vitamins**: **B3** (nicotinamide or niacin) & **B6** (pyridoxal)
  - It binds to and inhibits the enzymes that converts these vitamins to other metabolites
  - This results in inhibiting the synthesis of **mycolic acid**; a component of Mycobacteria cell wall (responsible for acid fastness)
- Isoniazid is **absorbed from GIT** & reaches all body tissues & fluids
- It is effective against **Mycobacteria** & has little effect on other bacteria
- INH as such is inactive & should be transformed by bacterial enzyme to the active form (**prodrug**)
  - Resistant mycobacteria stops producing the activating enzyme thus INH remains inactive. Since **resistance to INH is high**, it is usually given in combination with other 2 or 3 drugs such as rifampin & ethambutol

Antimicrobial Resistance

- Resistance to antimicrobials means that a microorganism previously susceptible to the action of antimicrobial is no longer affected by it
- Microbial resistance can arise as a result of genetic or non-genetic changes
- Non-genetic: e.g. tissue evasion or biofilm formation
- Genetic: it can be chromosomal or plasmid resistance
  - Chromosomal resistance: caused by mutations followed by natural selection
  - Plasmid resistance: transfer of resistance-gene-carrying plasmid from one bacteria to another (e.g. by conjugation)

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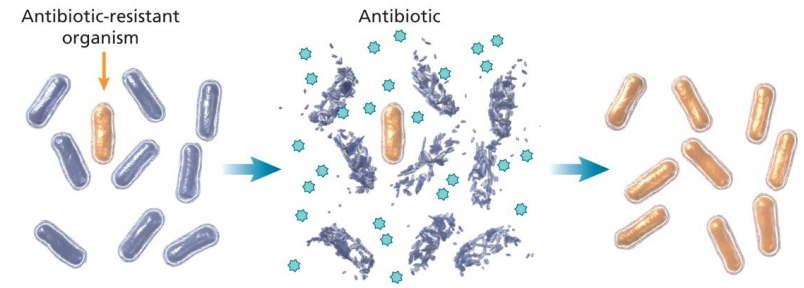

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Antimicrobial Resistance

- Mechanisms of antimicrobial resistance:
  - **Alteration of target site**: the antibiotic target site is modified so the antibiotic can no longer bind to it
  - **Decreasing the antibiotic permeability**: by changing membrane transport proteins so they don't transport the antibiotic inside the bacteria
  - **Production of efflux pumps**: which actively pumps the drug outside of the cell (active efflux); this is usually done by multiple drug resistance (MDR) protein which can produce resistance to multiple antibiotic types
  - **Production of inactivation enzymes**: these enzymes destroy or inactivate the antibiotic (e.g. β-lactamase)

Antimicrobial Resistance

- How to limit antimicrobial resistance?
  - Proper use of antimicrobials : (antimicrobial stewardship): prescription of antibiotics only when they are truly needed and using proper agent, dose and duration
  - The use of antibiotic combination: but only with agents having synergistic or additive effect
  - Limiting antibiotic use with farm animals (e.g. livestock)

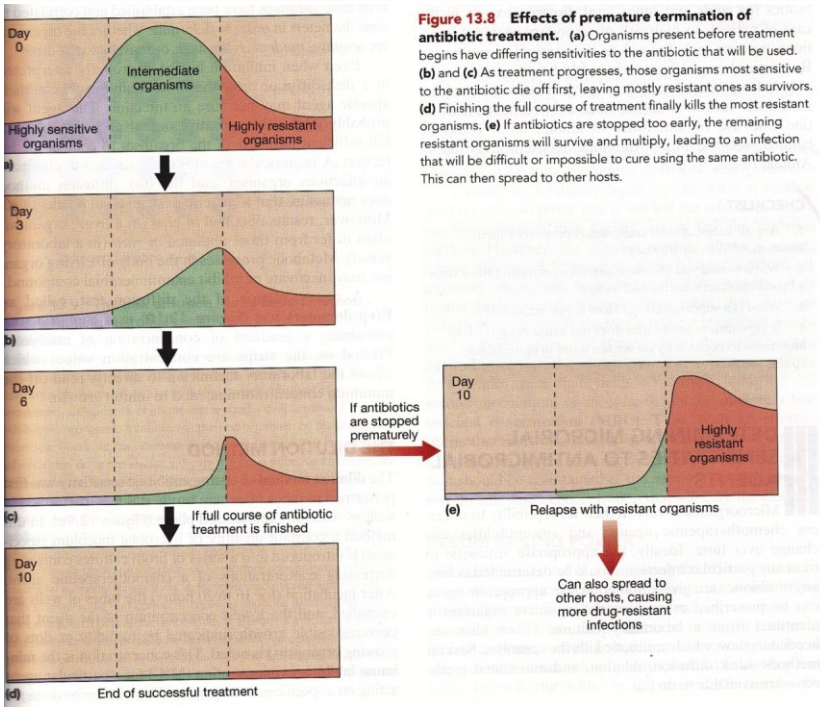

Figure 13.8 Effects of premature termination of antibiotic treatment. **(a)** Organisms present before treatment begins have differing sensitivities to the antibiotic that will be used. **(b)** and **(c)** As treatment progresses, those organisms most sensitive to the antibiotic die off first, leaving mostly resistant ones as survivors. **(d)** Finishing the full course of treatment finally kills the most resistant organisms. **(e)** If antibiotics are stopped too early, the remaining resistant organisms will survive and multiply, leading to an infection that will be difficult or impossible to cure using the same antibiotic. This can then spread to other hosts.