ANTIBIOTICS: BACK TO BASICS

Compiled by Dr Juanita Smit **February 2015**

An antimicrobial is an agent that kills microorganisms or inhibits their growth. Antimicrobial medicines can be grouped according to the microorganisms against which they primarily act. For example, antibacterials (commonly known as antibiotics) are used against bacteria and antifungals are used against fungi. They can also be classed according to their function. Antimicrobials that kill microbes are called *microbicidal;* those that merely inhibit their growth are called *microbiostatic.*

CLASSES OF ANTIBACTERIALS

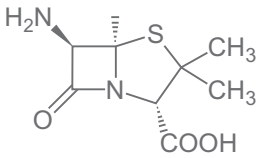
Beta-lactams

- Prevent bacteria from constructing a cell wall by binding to PBP (Penicillin-binding proteins). PBP are enzymes inside bacterial cells involved in the final stages (cross-linking of the peptide subunits) of peptidoglycan synthesis, which is the major component of bacterial cell walls.
- Contain a beta-lactam 'ring' which attaches to the active site of the bacterial enzymes.

Sub-categories: penicillins, cephalosporins, monobactams, carbapenems

Penicillins

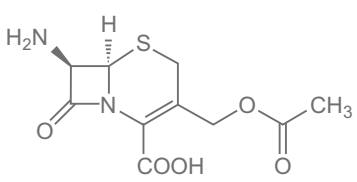
Alexander Fleming discovered penicillin by chance in 1928 when a mould grew on bacterial culture plates that he had not discarded.



- Penicillins are based on a chemical substance produced by the mould *Penicillium notatum*
- They are beta-lactams containing a nucleus of 6-aminopenicillanic acid and other ring side-chains
- Most have "-cillin" on the end of their name
- Subdivided into spectra according to their target organism
- Mostly used against Gram-positive bacteria, but attempts have been made to extend their spectrum
- Some have been developed semi-synthetically with different side-chains to give different properties: oral administration rather than by injection; to avoid breakdown by bacterial penicillinase (beta-lactamase) enzymes produced by penicillin-resistant bacterial strains
- Side-chains may contribute to side effects e.g. allergic reaction
- Some have been used in combination with a non-antibiotic compound with a similar structure to penicillin, that acts as an inhibitor of bacterial penicillinase
- MRSA has developed resistance to methicillin, flucloxacillin and other penicillins by also having an altered penicillin-binding protein

Cephalosporins

In 1945, Giuseppe Brotzu isolated a fungus *Cephalosporium acremonium* from seawater near a sewage outflow in Cagliari, Sardinia, and showed that it killed *Salmonella typhi*. Unable to develop it further, he passed the fungal culture to the Oxford group responsible for penicillin. Edward Abraham extracted several cephalosporins, and used money from patenting them for several charitable purposes.



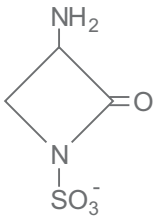
- Beta-lactams containing 7-aminocephalosporanic acid nucleus and a sidechain containing 3,6-dihydro-2H-1,3-thiazine rings
- Most have "Ceph-" or "cef- " at the beginning of their name
- Subdivided into five "generations" according to their target organism
- Initially used against Gram-positive bacteria, but later versions increasingly used against a wider range of pathogens (and less effective against Gram-positives)

- Less susceptible to penicillinases, but bacteria with extended-spectrum beta-lactamase (ESBL) have caused problems
- Some have been developed with a variety of side-chains in order to: avoid breakdown by bacterial beta-lactamase enzymes produced by penicillin-resistant bacterial strains; attach to different PBP; pass through the blood brain barrier; ionise to facilitate entry into Gram-negative bacterial cells.

1. **First generation**
   Moderate spectrum with activity against *Proteus mirabilis, Esherichia coli, Klebsiella pneumoniae;* not MRSA
   e.g. cephalexin
2. **Second generation**
   Moderate spectrum with anti-Haemophilus activity - against *Haemophilus influenza,* Neisseria
   e.g.cefuroxime
3. **Third generation**
   Broad spectrum e.g. ceftriaxone. Broad spectrum with anti-Pseudomonas activity e.g. ceftazidime
4. **Fourth generation**
   Broad spectrum with enhanced activity against Gram positive bacteria and ß-lactamase stability
   e.g. cefepime
5. **Fifth generation**
   Antipseudomonal and less susceptible to the development of resistance e.g. ceftobiprole

Monobactams

Discovered in 1979 as the result of "a novel screening procedure".



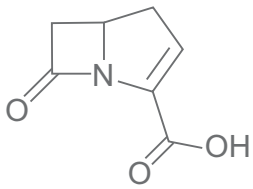
3-aminomonobactamic acid

- Based on a chemical substance produced by the bacterium *Chromobacterium violaceum*
- Contain a beta-lactam ring alone, not fused to another ring: based on 3-AMA (3 aminomonobactamic acid) - chemically similar to 6-APA
- Strong activity against susceptible gram-negative bacteria, including *Pseudomonas aeruginosa*
- Effective against a wide range of bacteria including *Citrobacter, Enterobacter, E. coli, Haemophilus, Klebsiella, Proteus, and Serratia* species
- No useful activity against gram-positive bacteria or anaerobes
- Must be injected or inhaled

Only real example: aztreonam

Carbapenems

This is a group of antibiotics released from 1985 and seen as our last effective defence against multi-resistant bacterial infections, but carbapenem resistance itself is now a cause for concern.

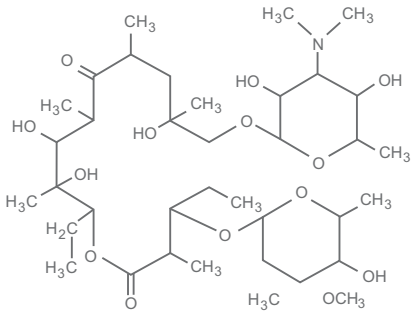


- Carbapenems are based on a chemical substance produced by the actinomycete *Streptomyces cattleya*
- Similar in structure to the penicillins, but with a carbon atom in position 1 instead of sulphur (hence the name)
- Most have "-penem" on the end of their name
- Broadest antibacterial spectrum of beta-lactams - active against both Gram positive and Gram negative bacteria, and anaerobes
- One of the antibiotics of last resort for many bacterial infections, and mainstay of therapy in patients with serious hospital-acquired infection
- Must be injected
- **Carbapenem antibiotic resistance** originates from Asia
- Carbapenem resistance due to genes on plasmids can be passed amongst different species

Examples: Meropenem, Imipenem + Cilastin (to prevent kidney damage)

Macrolides

In 1952 erythromycin was isolated by Eli Lilly's research team, led by J. M. McGuire, from the metabolic products of a strain of fungus *Saccharopolyspora erythraea* found in Filipino soil samples.



- Macrolides act as bacterial protein synthesis inhibitors
- Bind to the bacterial ribosome, preventing addition of amino acids to polypeptide chains
- Based on a chemical substance produced by the *actinomycete Saccharopolyspora erythraea*
- 14-, 15-, or 16-membered macrocyclic lactone rings with unusual deoxy sugars L-cladinose and D-desosamine attached
- Most have "-omycin" on the end of their name
- Different compounds produced by substitution of side groups onto erythromycin
- Antimicrobial spectrum slightly wider than that of penicillins
- May be used for people who have an allergy to penicillins
- Used at lower doses, may reduce inflammation by adjusting the immune response
- May build up in the body due to the liver recycling it in bile
- *Streptococcus pneumoniae* and other species have developed resistance

Examples: Erythromycin, Azithromycin

Tetracyclines

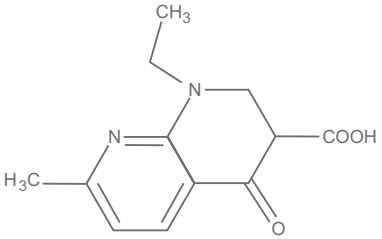
In 1945, at the age of 73, Benjamin Duggar discovered chlortetracycline (Aureomycin), the first of the tetracycline antibiotics, from a soil bacterium growing in allotment soil.

- Tetracyclines act as bacterial protein synthesis inhibitors
- Bind to the bacterial ribosome, preventing addition of amino acids to polypeptide chains
- Based on chemical substances produced by various Streptomyces species
- 4 hydrocarbon rings
- Most have "-cycline" on the end of their name
- Some naturally produced, some semi-synthetically produced by substitution of side groups
- Originally quite a wide antimicrobial spectrum, but resistance is now a problem
- May be used in the control of other non-microbial parasites in malaria and elephantiasis
- Side effects sometimes cause problems
- Food reduces the absorption of tetracycline, so it should be taken at least two hours before or after meals

Examples: Doxycycline

Quinolones

Nalidixic acid was discovered in the early 1960s during research of antimalarial agents - it was a by-product of the synthesis of chloroquine. Since then, more than 10,000 analogues and derivative compounds have been developed and more than 800 million patients have been treated with quinolones.



- Quinolones interfere with DNA replication and transcription in bacteria
- All synthetic compounds containing the quinolone nucleus or the naphthyridone nucleus, both ring structures
- Many have "-oxacin" on the end of their name (fluoroquinolones: "-floxacin")
- Development has produced four generations, with extra ring structures and substituents, extending their antimicrobial spectrum, particularly versus anaerobic bacteria
- Side effects sometimes cause problems
- Numerous pathogens now exhibit resistance worldwide

Examples: Ciprofloxacin, Levofloxacin

Aminoglycosides

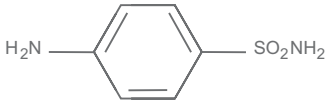
Selman A. Waksman, professor of biochemistry and microbiology at Rutgers University New Jersey USA, was interested in screening soil micro-organisms and led a team that discovered over twenty antibiotics, as well as coining the term antibiotic. He was credited with the discovery of streptomycin, which has been greatly used against *Mycobacterium tuberculosis.* In actual fact he had little to do with it; it was Albert Schatz, then a 23-year old graduate student in his laboratory, returning from war duty and inspired to find an antibiotic to treat tuberculosis, who first isolated streptomycin in 1943, essentially working in isolation. After the major commercial success of streptomycin, Schatz had to sue Waksman in order to be (at least partially) credited with the discovery. In 1994, Schatz was awarded the Rutgers medal for his work on developing streptomycin.

- Act as bacterial protein synthesis inhibitors
- Compounds of (usually 3) amino-sugars connected by glycosidic bonds of the *Streptomyces* (with the suffix -mycin) or *Micromonospora* (suffix -micin) genus
- Side effects sometimes cause problems

Examples: Streptomycin, Neomycin

Sulphonamides/sulfonamides (sulpha/sulfa drugs) and Trimethoprim

Although these are antibacterial or antimicrobial, they are often described as chemotherapeutic rather than antibiotic because they are synthesised chemically.

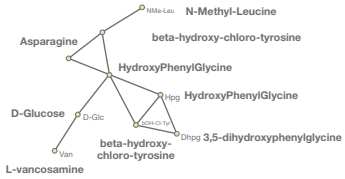


- The sulphonamide group acts as an analogue of PABA (para-amino benzoic acid) which is involved in folate synthesis, thus starving the bacteria of the B-group vitamin folate
- Sulfanilamide (an intermediate in the dye-making industry) has several clinical disadvantages which can be reduced by adding different side chains
- Possible side effects include hypersensitivity (allergic reactions), liver and kidney damage

Examples: Cotrimoxazole

Glycopeptides

In 1956 Dr. E. C. Kornfeld, organic chemist at Eli Lilly, isolated vancomycin (as compound 05865) from a soil sample containing *Streptomyces orientalis* from the Borneo jungle.

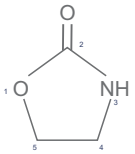


- Produced during fermentation by various micro-organisms
- Prevent bacterial cell wall synthesis (different mechanism to penicillin)
- Structure: glycosylated -, cyclic- or polycyclic nonribosomal peptides
- Most include amino acids differing from the normal 20 in proteins, perhaps connected by bonds other than peptide or disulfide bonds
- Used against Gram positive microorganisms
- Toxicity of early isolates ("Mississippi mud" - contained impurities) slowed down early development
- Vancomycin-resistant enterococci (VRE) emerged in the mid-1980s
- Vancomycin-resistant staphylococci emerged in the mid-1990s
- Vancomycin and related compounds were considered as drugs of last resort for treating MRSA

Examples: vancomycin, teicoplanin,

Oxazolidinones

Oxazolidinones are heterocyclic organic compounds, some of which were found to have antibiotic properties in the mid 1980s. Since resistance to other types of antibiotics had become a problem, these compounds were given special attention.



- Entirely synthetic
- Based on the 5-membered oxazolidinone ring containing both nitrogen and oxygen
- Act as protein synthesis inhibitors
- Used against Gram positives

Example: Linezolid