

## Antibiotics

### Definitions

Antibiotic are antimicrobial agents produced by micro-organisms that kill or inhibit other micro-organisms  
Chemotherapeutic agents are antimicrobial agents of synthetic origin useful in the treatment of microbial or viral disease. eg. sulfonilamides, isoniazid, ethambutol, chloramphenicol.

### 1. Inhibitors of Cell Wall Synthesis

- Prokaryotes differ from eukaryotes by having a cell wall that includes a peptidoglycan layer
- Gram Negatives have a thin layer covered by the lipopolysaccharide (endotoxin)
- Gram Positives have a thick layer with no such covering
- Peptidoglycan consists of multiple amino-sugars that alternate N-acetylglucosamine and N - acetylmuramic acid, which are cross linked to form a lattice
- Cross-linking is essential to resist the high internal osmotic pressures that are generated
- Peptidoglycan components manufactured intracellularly and transported across the cell membrane, where they link by transpeptidation

### Beta-Lactam Antibiotics - Penicillins

- Penicillins, Cephalosporins, Carbapenems and monobactams
- In 1928, Alexander Fleming observed a fungal contamination of a plate of Staph Aureus
- The beta-lactam ring is derived from the amino-acids valine and cysteine
- A secondary amino group (RNH) determines the individual properties of these antibiotics
- They bind to penicillin binding proteins on the bacterial cell wall and inhibit transpeptidation of the peptidoglycan layer
- Active mainly against gram +ve's, they are bacteriocidal
- Resistance due to  $\beta$ -lactamases in Staphylococcus
- This can be overcome by Clavulanic acid
- Excreted in urine by renal tubular secretion
- Side effects include Hypersensitivity

### Beta-Lactam Antibiotics - Cephalosporins

- Cephalosporium fungus from sewer outlet in Sardinia- shown to inhibit Staph. aureus growth
- Three types of cephalosporins, N,C and P.
- The type C, is the basis for most of the cephalosporin family by addition of various sidechains to core  $\beta$ -lactam nucleus.
- Action same as penicillins- interferes with peptidoglycan synthesis.
- Resistant to  $\beta$ -lactamases, acid stable.
- Some are oral, but most are given parentally.
- Wide distribution after absorption- pleura, pericardium, joint fluid and across placenta.
- Cefuroxime, cefotaxime and ceftriaxone also cross blood brain barrier
- Elimination via renal tubular secretion and glomerular filtration, some are eliminated in bile
- Side effects include a Penicillin type hypersensitivity with 10% cross-reactivity. Nephrotoxicity and alcohol intolerance reported. Diarrhoea with oral route
- Broad spectrum activity against most Gram positive and some Gram negative activity

## Other $\beta$ -Lactam Antibiotics

- Carbapenems (eg Imipenen) - resistant to most  $\beta$ -lactamases, wide spectrum against gram negative and positive aerobic and anaerobic organisms
- Monobactams (aztreonam) - derived from the bacteria *Chromobacterium violaceum*

## Vancomycin

- Glycopeptide antibiotic that inhibits cell wall synthesis, by preventing new disaccharide-pentapeptide releasing from carrier lipid, preventing attachment to peptidoglycan layer
- Active against Gram positive, including methicillin resistant *S.Aureus* - Resistance is rare
- Not absorbed from gastrointestinal tract, excreted by glomerular filtration
- Ototoxicity and nephrotoxicity have been reported

## Metronidazole

- Effective against anaerobes and protozoa
- Good absorption so oral route is possible as well as intravenous
- Mechanism of action poorly understood, maybe production of intracellular superoxide and other toxic oxygen free radicals - some nuclease activity, so may cleave bacterial DNA

## Active Against Bacterial Protein Synthesis

- Ribosomes are the basic units of machinery for protein synthesis.
- Bacterial ribosomes have 50S and 30S subunits, mammalian ribosomes have 60S and 40S subunits
- mRNA attaches to 30S of ribosome - reads successive mRNA
- The next tRNA and attached aa, attach by complementary base-pairing to the mRNA 'A' site
- The P site contains tRNA with its bound peptide chain. The aa on the tRNA in the A site binds to the peptide chain at the P site by transpeptidation, the tRNA at the P site is ejected and the tRNA at the A site translocates to the P site

## Tetracyclines

- Broad spectrum, original derived from *Streptomyces*
- More recent compounds are semi-synthetic or synthetic (doxycycline, tetracycline)
- Block protein synthesis by competing with tRNA for the A site of the ribosome/ mRNA complex

## Chloramphenicol

- Originally from *Streptomyces*, but now synthetic
- Binds to the 50S subunit at same site as erythromycin, and inhibits transpeptidation
- Broad spectrum and bacteriostatic, crosses blood-brain barrier Problems with resistance due to chloramphenicol acetyl-transferase

## Erythromycin

- Inhibits translocation of ribosome along mRNA chain
- Spectrum similar to penicillins, used in penicillin allergies
- Bacteriostatic or bacteriocidal, oral or parenteral, good prostate penetration, poor synovial penetration and does not cross blood-brain barrier
- Side effects are rare

## Aminoglycosides

- Bind to 30S subunit and prevent complexing of the 50S subunit
- Bacteriocidal
- Effects enhanced by agents that interfere with cell wall synthesis
- Not absorbed from GI tract. Do not cross BB barrier
- Plasma half-life of 2-3 hours, eliminated entirely by glomerular filtration.
- Good for Gram negative and some Gram positive organisms, no effect on anaerobe
- Some resistance due to microbial inactivating enzymes
- Nephrotoxicity and ototoxicity, very rarely- neuromuscular blockade
- Contra-indicated in Myasthenia Gravis

## Inhibit DNA Synthesis

### Fluoro-Quinolones

- Synthetic antibiotics which act by inhibition of bacterial DNA gyrase (topoisomerase II)
- This is responsible for supercoiling of the DNA helix
- Prokaryotic DNA gyrase is structurally different from eukaryotic
- Bacteriocidal - Early drugs (nalidixic acid) active against Gram negative
- Newer forms (ciprofloxacin, ofloxacin and norfloxacin) = wider activity
- Absorbed orally with a half-life of 4 hours
- Side effects include gastric disturbances, skin rashes, CNS disturbances, blood dyscrasias, tendinitis

## AntiMetabolites

### 1.Sulphonamides

- Discovered in 1930. Prontosil, a dye, could protect mice from lethal doses of haemolytic streptococci
- Found to be pro-drug of sulphanilamide
- Modification of sulphonamide structure has produced thiazides, sulphones and oral hypoglycaemics
- Folate made from pABA in bacteria by dihydropterotate synthetase
- Bacteriostatic, problems with resistance, liver metabolised
- Side effects include Hypersensitivity, bone marrow depression, crystalluria and methaemaglobinaemia

### 2.Trimethoprim

- Folate antagonist
- Bacteria must synthesise folate which is converted to tetrahydrofolate by dihydrofolate reductase.
- Trimethoprim inhibits this enzyme - Differential sensitivity to this in humans and bacteria
- The IC50 ( $\mu\text{mol/l}$ ) is 0.005 and 260, for bacteria and humans
- Bacteriostatic, good against gram negative's - given in combination with sulphonamide
- Side effects include skin rashes, gastric upset and folate deficiency

### Nitrofurantoin

- Synthetic compound with broad spectrum across gram -ve and +ve
- Inhibits Bacterial Folate Synthesis
- Rapid excretion in high urine concentrations, so only used for urinary tract infections
- Works better in acidic urine
- Side effects are rare and include mainly gastric upset or hypersensitivity skin rash