CHEMOTHERAPY

ANTI-BACTERIAL AGENTS

Dr Sindwa Kanyimba
Lecturer, Pharmacology

ANTI-BACTERIAL AGENTS

INTRODUCTION:

Bacteria belong to the kingdom of prokaryotic organisms

Some bacteria are pathogenic to humans and responsible for a number of medically important diseases

Chemotherapy for bacterial infections aims to selectively target the invading bacteria while having minimal effect on the host. This is achieved by exploiting differences that exist between the structure and physiology of the prokaryotic bacterial cells and the host eukaryotic cell.

ANTI-BACTERIAL AGENTS

INTRODUCTION …. CONT'D:

Anti-bacterial agents can be:

- Bacteriostatic: Inhibit bacterial growth but do not kill the bacteria
- Bactericidal: Kill bacteria

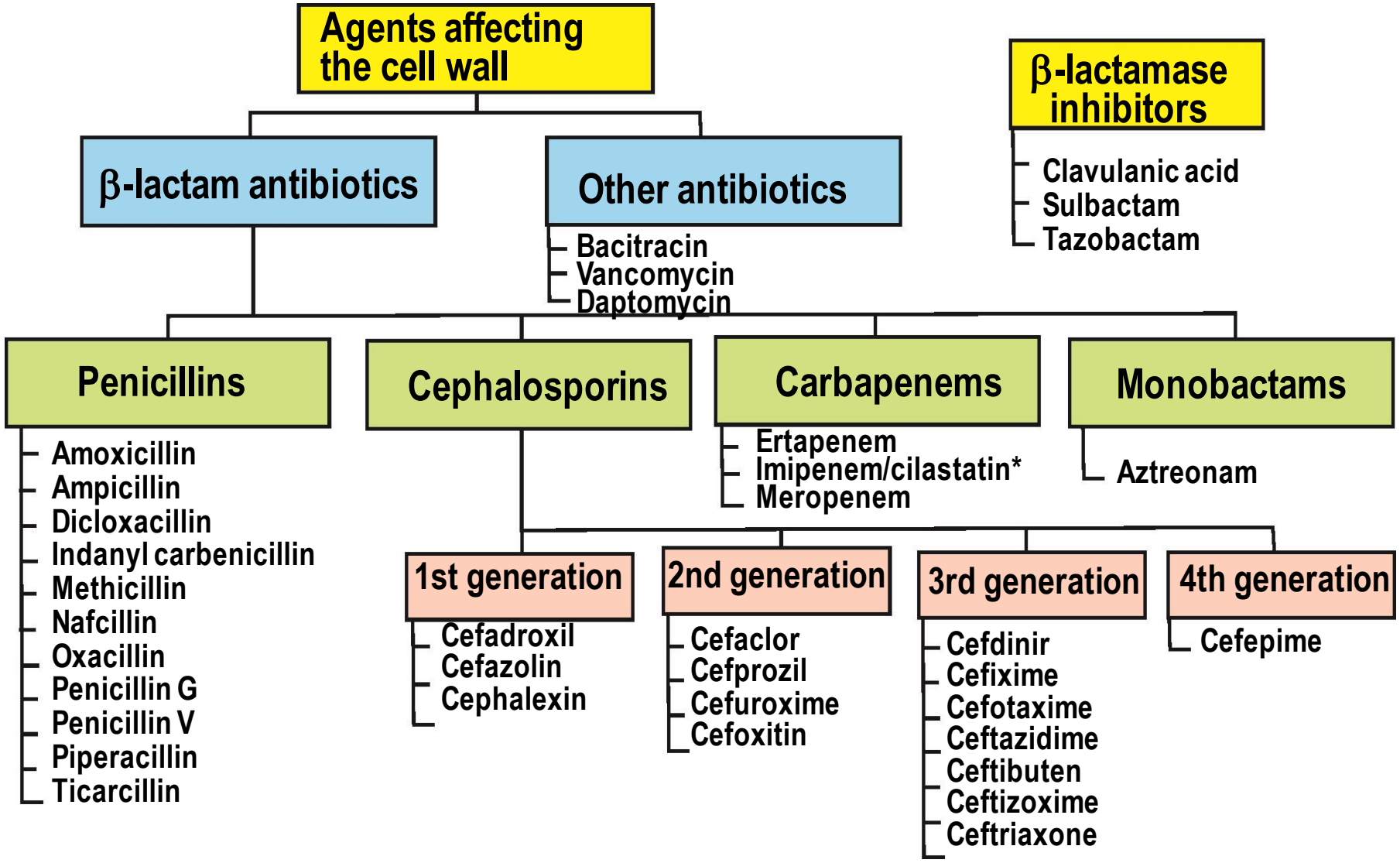
ANTI-BACTERIAL AGENTS

LEARNING OBJECTIVES:

1. Classify anti-bacterial drugs according to chemical structure and mechanisms of actions
2. Describe the mechanisms of action of various groups of anti-bacterial drugs
3. Describe the relevant clinical pharmacology (anti-bacterial spectrum, clinical indications, anti-microbial resistance, adverse effects, drug interactions, precautions and contraindications) of commonly used anti-bacterial drugs

BETA-LACTAM ANTI-BIOTICS AND OTHER CELL WALL SYNTHESIS INHIBITORS

SUMMARY OF ANTI-BACTERIAL AGENTS AFFECTING CELL WALL SYNTHESIS



(according to Lippincott´s Pharmacology, 2009)

ANTI-BACTERIAL DRUGS THAT INHIBIT CELL WALL SYNTHESIS

- Are bactericidal
  - selectively interfere with synthesis of the bacterial cell wall a structure that mammalian cells do not possess
  - The cell wall is a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links
- Require actively proliferating micro-organisms to be maximally effective

PENICILLINS: MECHANISM OF ACTION

Inhibition of transpeptidase

Penicillins inactivate bacterial transpeptidases and prevent the cross-linking of peptidoglycan polymers essential for bacterial cell wall integrity. This results in loss of rigidity and a susceptibility to rupture.

NB: Penicillins are inactive against organisms that do not have peptidoglycan structure in their cell wall (e.g. mycobacteria)

PENICILLINS: MECHANISM OF ACTION …. CONT'D

Production of autolysins

- Gram positive cocci produce degradative enzymes, autolysins. (autolysins participate in the remodeling of the bacterial cell wall)
- In the presence of penicillins , the degradative action of the autolysins proceeds in the absence of cell wall synthesis and further weakens the cell wall

MECHANISMS UNDERLYING BACTERIAL RESISTANCE TO BETA-LACTAMS

- Production of β-lactamase which degrades beta-lactams
- Alteration in penicillin binding proteins (PBP)
- Decreased entry of β-lactams (cell membrane and cell wall structure; porin mechanism)
- Increased efflux of β-lactams

CLASSIFICATION OF PENICILLINS

1. Prototype penicillin: penicillin G and penicillin V
2. Penicillinase resistant: methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin (narrow spectrum activity against staphylococci)
3. Extended spectrum penicillins (aminopenicillins): ampicillin, amoxicillin (activity similar to prototype penicillins but with greater gram negative bacteria coverage)
4. Anti-pseudomonal penicillins: carbenicillin, ticarcillin, piperacillin (more active against gram negative rods including pseudomonas aeruginosa, but less active against other bacteria)

PENICILLIN G

- Spectrum: Most gram-positive cocci, gram positive rods (bacilli) and gram-negative cocci (gonococci and meningococci), spirochetes and most anaerobes (except bacteroides fragilis)
- Susceptible to inactivation by beta-lactamases
- Unstable in low pH therefore given parenterally

FORMS OF PENICILLIN G

Benzyl penicillin

Short acting form

Given IV or IM

Procaine penicillin G and benzathine penicillin G

- These are suspensions of penicillin G that prolong its half-life allowing a reduced frequency of injections
- Given deep IM, they release penicillin slowly from the site
- Procaine penicillin is given 12-24 hourly while a single injection of benzathine penicillin is effective for 3-4 weeks

PENICILLIN V (PHENOXYMETHYLPENICILLIN)

- Spectrum similar to penicillin G
- Not used for treatment of septicemia because of its higher minimum bactericidal concentration
- Is more acid-stable than penicillin G therefore given orally

ANTI-STAPHYLOCOCCAL PENICILLINS

- Include: methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin and flucloxacillin
- Are resistant to penicillinase
- Narrow spectrum penicillins used for the treatment of infections caused by penicillinase-producing staphylococci
- Some staphylococcus strains are resistant to these penicillins – referred to as methicillin-resistant strains (MRSA). They are usually susceptible to vancomycin (rarely to ciprofloxacin, rifampicin)

AMINO-PENICILLINS: AMPICILLIN AND AMOXICILLIN

- Have extended spectrum of activity with broadened gram negative coverage
- Spectrum similar to penicillin G, but are more effective against some gram-negative bacilli - Hemophilus influenzae, E. Coli
- Amoxicillin is similar to ampicillin but has better oral absorption
- They are useful for infections caused by haemophilus influenzae, pneumococcus, streptococcus pyogenes, meningococcus, proteus mirabilis and enterococcus faecalis

AMPICILLIN AND AMOXICILLIN …. CONT'D

- Amoxicillin is commonly used for endocarditis prophylaxis before major surgical procedures and oral surgery
- Ampicillin is the drug of choice for the gram-positive bacillus Listeria monocytogenes
- Resistance is a problem because of their inactivation by plasmid-mediated penicillinase (E. coli and H. influenzae are frequently resistant)
- Formulation with a beta-lactamase inhibitor (e.g. clavulanic acid, sulbactam) can protect them from the enzymatic inactivation

UREIDO-PENICILLINS

Piperacillin

- Effective against P. aeruginosa as well as a large number of gram-negative organisms
- It is susceptible to breakdown by beta-lactamase – thus formulated with tazobactam a beta-lactamase inhibitor

Mezlocillin and azlocillin

Similar to piperacillin

MECILLINAM

- A penicillin that is more active against Gram-negative enteric bacteria
- Hydrolyzed by beta-lactamases
- Pivmecillinam is a pro-drug, hydrolyzed to mecillinam

BETA-LACTAMASE INHIBITORS

- Clavulanic acid, sulbactam, tazobactam : contain a beta lactam ring, but do not have significant antibacterial activity
- Bind to and inactivate beta-lactamases (however, not all beta-Iactamases are inhibited e.g. tazobactam does not affect P. aeruginosa beta-lactamase). Therefore, this organism remains refractory to piperacillin.
- By inactivating beta-lactamase these compounds enhance the antibacterial activity when used in combination with other β-lactam antibiotics

BETA-LACTAMASE INHIBITORS …. CONT'D

Examples of penicillin + beta-lactamase inhibitor combinations

- Amoxicillin + clavulanic acid (co-amoxiclav)
- Ticarcillin + clavulanic acid
- Piperacillin + tazobactam
- Ampicillin + sulbactam

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

- MRSA is a bacterium responsible for several difficult-to-treat infections in humans. It is also called oxacillin-resistant Staphylococcus aureus (ORSA)
- MRSA is any strain of Staphylococcus aureus that has developed, through the process of natural selection, resistance to beta-lactam antibiotics, which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, cloxacillin etc) and the cephalosporins.

MRSA …. CONT'D

- MRSA develops due to a resistance gene which stops β-lactam antibiotics from inactivating the enzymes (transpeptidases) critical for cell wall synthesis. The gene encodes penicillin-binding protein 2a (PBP2a), which does not bind methicillin or other β-lactam antibiotics, unlike the normal PBPs.
- Antimicrobial agents active against MRSA include vancomycin, rifampicin and ciprofloxacin

PENICILLINS: PHARMACOKINETICS

Route of administration

Determined by the stability of the drug to gastric acid and by the severity of the infection

- Only oral formulations: penicillin V and amoxicillin
- Only parenteral formulations: penicillin G, ureido-penicillins
- Depot forms: procaine penicillin G and benzathine penicillin G (administered IM; serve as depot forms: slowly absorbed into the circulation and persist at low levels over a long time period)
- Both parenteral and oral: ampicillin, amoxicillin-clavulate

PENICILLINS: PHARMACOKINETICS …. CONT'D

Absorption

- Incomplete for most penicillins after oral administration
- Reach the intestine in sufficient amounts to affect the composition of the intestinal flora
- Amoxicillin is almost completely absorbed
  - For this reason, it is not appropriate therapy for the treatment of salmonella-derived enteritis because therapeutically effective levels do not reach the organisms in the intestinal crypts

PENICILLINS: ABSORPTION …. CONT'D

- Absorption of penicillin V and all the penicillinase-resistant penicillins is reduced by food in the stomach – thus they must be administered 30-60 minutes before meals or 2-3 hours postprandially
- Absorption of amoxicillin and ampicillin is less affected by food

PENICILLINS: PHARMACOKINETICS …. CONT'D

Distribution

- All penicillins cross the placental barrier (but none have been shown to be teratogenic)
- Penetration into certain sites is insufficient e.g. bone or cerebrospinal fluid. Levels in the prostate are insufficient to be effective against infections.
- Penetration into tissues is increased during inflammation e.g. meningitis

Metabolism

- Host metabolism of the beta-Iactam antibiotics is usually insignificant

PENICILLINS: EXCRETION

Kidney

- Tubular secretion and glomerular filtration
- Patients with impaired renal function - adjust dosage regimens. Half-life of penicillin G can increase from a normal of 0.5-1.0 hour to 10 hours in renal failure.
- Probenecid inhibits the active tubular secretion of penicillins

Biliary route

- Nafcillin is excreted via the biliary route
- This is also the preferential route of excretion for the ureido-penicillins in cases of renal failure

PENICILLINS: ADVERSE EFFECTS

Hypersensitivity reactions (types I-IV):

- The most important adverse reaction associated with penicillins
- The major cause is metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction
- Incident: 10% of patients have some kind of reaction
- There is cross allergic reactions among the beta-lactam antibiotics

PENICILLINS: ADVERSE EFFECTS …. CONT'D

- Diarrhea: Especially in agents that are incompletely absorbed or with extended spectrum. Pseudomembranous colitis may occur with broad spectrum penicillins.
- Nephritis: Acute interstitial nephritis with high doses of methicillin
- Neurotoxicity: Penicillins are irritating to neuronal tissue and can provoke seizures if injected intrathecally or if very high blood levels are reached - epileptic patients are especially at risk
- Cation toxicity: Penicillins are generally administered as the sodium or potassium salt, and hypernatremia or hyperkalaemia can occur

CLINICAL USES OF PENICILLINS

- Bacterial meningitis caused by N. meningitidis, S. pneumoniae: penicillin G (benzylpenicillin given IV in high does)
- Bone and joint infections caused by S. aureus: flucloxacillin
- Skin and soft tissue infections caused by S. pyogenes or S. aureus: benzylpenicillin, flucloxacillin
- Animal bites: co-amoxiclav
- S. pyogenes pharyngitis: phenoxylmethyl penicillin (penicillin V)
- Otitis media caused by S. pyogenes and H. influenzae: amoxicillin

CLINICAL USES OF PENICILLINS …. CONT'D

- Bronchitis (mixed infections common): amoxicillin
- S.Pneumoniae pneumonia: amoxicillin
- Urinary tract infections (e.g. with E. coli): amoxicillin
- Syphilis: procaine or benzathine penicillin
- Endocarditis (e.g. with Streptococcus viridans or Enterococcus faecalis): penicillin G
- Serious infections with P. aeruginosa: piperacillin, carbenicillin, tircacillin

CEPHALOSPORINS

- Beta-lactam antibiotics that are closely related both structurally and functionally to the penicillins
- Mostly semi-synthetic
- Mechanism of action: same as penicillins
- Same resistance mechanisms as penicillins - however, they tend to be more resistant than the penicillins to beta-lactamases

CEPHALOSPORINS: ANTI-BACTERIAL SPECTRUM

- Classified as first, second, third, fourth and fifth generation
- Based largely on their bacterial susceptibility patterns and resistance to beta-lactamases
- All cephalosporins are ineffective against MRSA (except 5th generation cephalosporins like ceftaroline and ceftobiprole), Listeria monocytogenes, Clostridium difficile and the enterococci

CEPHALOSPORINS: FIRST GENERATION

- Include cephalexin, cephalothin, cefazolin and cefadroxil
- Active mostly against gram positive bacteria
- Resistant to the staphylococcal penicillinase
- Have some activity against Proteus mirabilis, E. coli, and Klebsiella pneumoniae

CEPHALOSPORINS: SECOND GENERATION

- Include cefuroxime, cefoxitin, cefaclor and cefotetan
- Greater activity against three additional gram negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species
- Effective against anaerobes including Bacteroides fragilis; cefoxitin is the most active against B. fragilis
- Activity against gram-positive organisms is weaker than first generation cephalosporins

CEPHALOSPORINS: THIRD GENERATION

- Inferior to first and second generation cephalosporins in activity against gram positive bacteria
- Enhanced activity against gram-negative bacilli and most other enteric organisms plus Serratia marcescens
- Include: ceftriaxone, cefotaxime (agents of choice in the treatment of bacterial meningitis), ceftazidime and cefoperazone (active against Pseudomonas aeruginosa) and cefpodoxime (given orally)

CEPHALOSPORINS: FOURTH GENERATION

- Include cefepime and cefpirom
- Only parenteral
- Wide spectrum of activity: active against streptococci and staphylococci (but not MRSA), aerobic gram negative organisms (enterobacter, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa)

CEPHALOSPORINS: FIFTH GENERATION

- Ceftobiprole: Active against MRSA, penicillin-resistant Streptococcus pneumoniae, Pseudomonas aeruginosa, and enterococci (including vancomycin resistant enterococci)
- Ceftaroline: Active against MRSA and gram-positive bacteria. It retains the activity of later-generation cephalosporins having broad-spectrum activity against gram-negative bacteria. It does not have the antipseudomonal or VRE coverage of ceftobiprole.
- Ceftolozane: Developed for the treatment of infections with gram-negative bacteria that have become resistant to conventional antibiotics. Is a new option for treatment of complicated intra-abdominal infections and complicated urinary tract infections. Ceftolozane is combined with the β-lactamase inhibitor tazobactam to prevent its degradation.

CEPHALOSPORINS: PHARMACOKINETICS

- Some are given orally, most IV or IM
- All distribute very well into body fluids (adequate therapeutic levels in the CSF only with the third-generation cephalosporins ceftriaxone and cefotaxime)
- Cefazolin is able to penetrate bone (thus used for prophylaxis in dentistry and orthopedics prior to surgery because of its half-life and activity against penicillinase-producing S. aureus)

CEPHALOSPORINS: PHARMACOKINETICS

- All cephalosporins cross the placenta but are not teratogenic
- Elimination is through tubular secretion and/or glomerular filtration (doses must be adjusted in severe renal failure)
- Cefoperazone and ceftriaxone are excreted in bile into the feces - thus are frequently employed in patients with renal insufficiency)

CEPHALOSPORINS: ADVERSE EFFECTS

- Hypersensitivity reactions: patients who have had an anaphylactic response to penicillins should not receive cephalosporins. Use with caution in individuals who are allergic to penicillins - about 15 % show cross-sensitivity. In contrast, the incidence of allergic reactions to cephalosporins is 1-2 % in patients without a history of allergy to penicillins.
- Disulfiram-like effect is seen with cefamandole, ceftriaxone and cefoperazone if ingested with alcohol or alcohol-containing medications. They block the acetaldehyde dehydrogenase

CEPHALOSPORINS: ADVERSE EFFECTS

- Bleeding: due to anti-vitamin K effects (corrected by administration of vitamin K)
- Nephrotoxicity (especially when administered with diuretics)
- Superinfection with gram positive organisms and fungi (cephalosporins are the number one cause of hospital acquired C. difficile colitis)

CEPHALOSPHORINS: CLINICAL USES

First generation

- E. Coli and klebsiella infections
- Penicillin and sulfonamide resistant urinary tract infections
- Prophylaxis in various surgical procedures

Second generation

- Streptococcal, E.coli, klebsiella, proteus spp and anaerobe infections (except C.difficile)
- Used in the management of UTIs, RTIs, bone and soft tissue infections
- Except cefuroxime, they do not penetrate CSF

CEPHALOSPHORINS: CLINICAL USES …. CONT'D

Third generation

- Pseudomonas aeruginosa infections (cefoperazone and ceftazidime)
- Empiric therapy for community acquired meningitis (ceftriaxone)
- Hospital acquired gram negative infections (alone or in combination with an aminoglycoside)
- Lyme disease
- Gonorrhoea (ceftriaxone)
- Gram negative septicaemia

Fourth generation

- Gram negative bacteria infections (including pseudomonas aeruginosa)

BETA-LACTAM RELATED COMPOUNDS

- Include carbapenems and monobactams
- Structurally similar to β-lactam antimicrobial agents, but lacks the classical ring structures of β-lactams. In terms of anti-microbial activities they share those of other beta-lactam antibiotics.

CARBAPENEMS

- Include: imipenem-cilastatin, meropenem, ertapenem, doripenem
- Imipenem is marketed in combination with cilastatin, an inhibitor of renal dehydropeptidase I (an enzyme which inactivates imipenem)
- Have broad-spectrum activity including penicillinase producing gram positive and gram negative organisms, anaerobes and P. aeruginosa, and are used to treat infections caused by these organisms

CARBAPENEMS …. CONT'D

- Are relatively resistant to beta-lactamases and do not have exhibit cross-resistance with other antibiotics
- Administered IV
- Penetrate well into CNS
- Excreted by glomerular filtration (adjust doses in renal insufficiency)
- Adverse effects: nausea, vomiting, and diarrhea, eosinophilia and neutropenia (less common). High levels (especially imipenem) may provoke seizures.

MONOBACTAMS: AZTREONAM

- Highly resistant to the action of beta-lactamases
- Spectrum: active against P. aeruginosa and other gram negative bacteria thus used for infections caused by these organisms
- Lacks activity against gram-positive organisms or anaerobes
- Used only for combination with other antibacterial drugs in empiric therapy

AZTREONAM …. CONT'D

- Given IV or IM
- Excreted in the urine (can accumulate in patients with renal failure)
- Adverse effects: may cause phlebitis, skin rash, and occasionally, abnormal liver function tests
- Has low immunogenic potential, little cross-reactivity with antibodies induced by other beta-lactam antibiotics

OTHER INHIBITORS OF BACTERIAL CELL WALL BIOSYNTHESIS

Glycopeptides

- Include vancomycin and teicoplanin
- Mechanism of action: inhibit cell wall synthesis - prevents the transglycosylation step in peptidoglycan polymerization
- Are bactericidal
- Indications: gram positive bacteria, MRSA, enterococcal infections and pseudomembranous colitis caused by Clostridium difficile
- Vancomycin acts synergistically with the aminoglycosides: the combination can be used in the treatment of enterococcal endocarditis individuals with prosthetic heart valves

VANCOMYCIN

- Given by slow IV infusion for systemic infections or for prophylaxis
- Not absorbed after oral administration: oral vancomycin use is thus limited to the treatment of antibiotic-associated colitis due to C. difficile or staphylococci
- Inflammation allows penetration into the meninges (often necessary to combine with another antibiotic in the treatment of meningitis e.g., ceftriaxone)

VANCOMYCIN …. CONT'D

Elimination

90 - 100 % excreted by glomerular filtration (normal half-life: 6-10 hours; over 200 hours in end-stage renal disease; adjust dosage in renal failure – accumulation of the drug occurs)

Adverse effects

Fever, chills, phlebitis at the injection site, flushing ("red man syndrome"), shock when administered rapidly, rashes, and ototoxicity and nephrotoxicity (more common when administered with other drug (e.g., an aminoglycoside) that can also produce these effects)

DAPTOMYCIN

- Mechanism: depolarisation of the cell membrane resulting in potassium efflux and death; and inhibition of DNA, RNA, protein synthesis. It is bactericidal.
- Spectrum: similar to vancomycin
- Indication: treatment of resistant gram positive bacteria incl. MRSA and vancomycin-resistant enterococci. Used in the treatment of complicated skin infection, endocarditis, and bacteremia by S. aureus [not for pneumonia (inactivated by pulmonary surfactant)]

DAPTOMYCIN …. CONT'D

- Given as IV infusion
- It is eliminated renally and is not metabolized (adjust dosage in renal impairment)
- Adverse effects: myopathy (discontinue statins), constipation, nausea, headache, insomnia, elevated hepatic transaminases

MISCELLANEOUS CELL WALL SYNTHESIS INHIBITORS

Cycloserine

- Inhibits the incorporation of alanine into the peptidoglycan pentapeptide
- Active against mycobacteria and gram negative bacteria
- Used only as second line drug for treatment of UTIs and tuberculosis
- Given orally
- Adverse effects: seizures and acute psychosis

MISCELLANEOUS CELL WALL SYNTHESIS INHIBITORS …. CONT'D

Bacitracin

- Most active against gram positive bacteria
- Used only topically in combination with neomycin or polymixin for minor infections

QUINOLONES, TETRACYCLINES, CHLORAMPHENICOL, MACROLIDES, CLINDAMYCIN & LINEZOLID

QUINOLONES

Include:

Nalidixic acid, ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, moxifloxacin, gatifloxacin, lomefloxacin, gemifloxacin and sparfloxacin. All are flouroquinolones except nalidixic acid

Mechanism of action

Inhibit bacterial DNA gyrase (topoisomerase II) and topoisomerase IV and thereby inhibit the replication of bacterial DNA. Are bactericidal

QUINOLONES: ANTI-BACTERIAL SPECTRUM

- Nalidixic acid: Has moderate activity against gram negative organisms
- Ciprofloxacin, ofloxacin, levofloxacin, norfloxacin and lomefloxacin are highly active against gram negative bacteria and moderately active against gram positive bacteria. Also have some activity against atypical bacteria (mycoplasma, chlamydia, legionella).
- Ciprofloxacin is active against bacillus anthracis

QUINOLONES: ANTI-BACTERIAL SPECTRUM …. CONT'D

- Moxifloxacin, gatifloxacin, sparfloxacin and gemifloxacin have an even greater activity against gram positive organisms and activity against some anaerobes, and improved activity against atypical bacteria
- Gatifloxacin, moxifloxacin, levofloxacin and ofloxacin are also active against mycobacterium tuberculosis and can be used as second-line treatment for tuberculosis

CIPROFLOXACIN

- Against many systemic infections (excepting serious infections by MRSA, enterococci, and pneumococci)
- Useful in treating infections caused by many Enterobacteriaceae and other gram negative bacilli (e.g. traveler's diarrhea caused by E. coli)
- Drug of choice for prophylaxis and treatment of anthrax and drug of choice for typhoid fever
- The most effective of the fluoroquinolones for P. aeruginosa infections

NORFLOXACIN

- Not effective in systemic infections
- More effective than nalidixic acid, active against both gram-negative (including Pseudomonas aeruginosa) and gram-positive organisms
- Used for complicated and uncomplicated UTIs and prostatitis

LEVOFLOXACIN

- An isomer of ofloxacin
- Primarily used in the treatment of prostatitis due to E. coli and of bacterial sexually transmitted diseases (excepting syphilis)
- An alternative therapy in patients with gonorrhea
- Very good activity against respiratory infections due to S. Pneumoniae

OTHER FLOUROQUINOLONES

Gatifloxacin

- Very good activity against respiratory infections due to S. pneumoniae

Moxifloxacin

- Enhanced activity against gram positive organisms (e.g. S. pneumoniae) and also excellent activity against anerobes (e.g. Bacteroides fragilis)
- Has very poor activity against P. aeruginosa

FLUOROQUINOLONES: ADVERSE EFFECTS

- GIT: the most common - nausea, vomiting, diarrhea
- CNS: headache and dizziness or light-headedness. Use with caution in patients with epilepsy – may evoke seizures.
- Phototoxicity
- Hepatotoxicity
- Connective tissue problems – tendinitis, tendon rupture
- Sparfloxacin and moxifloxacin prolong the QT interval

FLUOROQUINOLONES: CONTRAINDICATIONS

- Pregnancy, lactating mothers, and children under 18 years - articular cartilage erosion (arthropathy) occurs in immature experimental animals
- Sparfloxacin and moxifloxacin (prolong the QT interval) – avoid use in those who are predisposed to arrhythmias or are taking anti-arrhythmics

FLUOROQUINOLONES: DRUG INTERACTIONS

- The effect of antacids and cations (aluminium, calcium and magnesium) reduce absorption of flouroquinolones
- Inhibit cytochrome P450 enzymes - may raise the serum levels of warfarin, theophylline, caffeine, and cyclosporine
- Cimetidine reduces the metabolism of the fluoroquinolones

TETRACYCLINES

Include tetracycline, doxycycline, demeclocycline, minocycline and tigecycline

Entry into susceptible organisms is by passive diffusion and by an energy-dependent transport protein mechanism

Susceptible strains concentrate the tetracyclines intracellularly

Mechanism of action

Bind reversibly to the 30s subunit of the bacterial ribosome and block access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site

Are bacteriostatic

TETRACYCLINES: ANTI-MICROBIAL SPECTRUM

- Tetracyclines are broad spectrum antibiotics
- Active against both gram positive and gram negative bacteria
- Effective against intracellular bacteria - they are drugs of choice against atypical bacteria - rickettsia, mycoplasma and chlamydial
- Active against some protozoa – plasmodia, entamoeba histolytica

TETRACYCLINES: CLINICAL USES

- Use of tetracyclines in the treatment of many gram positive and gram negative bacterial infections has declined due to widespread resistance
- Tetracyclines are mainly used in the treatment of rickettsial infections, brucellosis, cholera, Lyme disease, mycoplasma infections, and chlamydial infections
- They are also used in acne vulgaris, helicobacter pylori eradication regimens, malaria and amoebiasis
- Minocycline can be used in combination regimens for the treatment of leprosy

TETRACYCLINES: RESISTANCE

- Resistance is plasmid-mediated and results primarily from a decreased ability to accumulate in bacteria and from the production of an inhibitor of the binding site for tetracyclines
- There is widespread cross resistance (any organism resistant to one tetracycline is resistant to most of the tetracyclines)
- The majority of penicillinase-producing staphylococci are now also insensitive to tetracyclines
- Tigecycline has activity against many tetracycline resistant organisms

TETRACYCLINES: PHARMACOKINETICS

- Completely absorbed orally and thus are given orally (except tigecycline which is given IV)
- Absorption is reduced by dairy products (due to calcium contained therein), antacids, and divalent and trivalent cations (calcium, magnesium and aluminium)
- Widely distributed to soft tissues, teeth and bones
- High penetration to the placenta

TETRACYCLINES: PHARMACOKINETICS …. CONT'D

- Insufficient entry into CNS (except minocycline)
- The primary route of elimination for most tetracyclines is the kidney
- Many tetracyclines undergo enterohepatic recirculation
- Doxycycline is excreted almost entirely via bile into the faeces and hence is the safest tetracycline to administer to individuals with impaired renal function

TETRACYCLINES: ADVERSE EFFECTS

- Nausea, vomiting and diarrhoea
- Epigastric distress; irritation of the gastric mucosa. Alleviated if the drug is taken with foods (avoid dairy foods)
- Deposition in the bone and primary dentition – occurs during calcification in growing children. There is discoloration and hypoplasia of the teeth and a temporary stunting of growth. Tetracyclines are therefore contraindicated in pregnancy and in children younger than 12 years.
- Hepatotoxicity

TETRACYCLINES: ADVERSE EFFECTS (CONT'D)

- Phototoxicity (more frequently with doxycycline and demeclocycline)
- Superinfections: (1) candida e.g. in the vagina (2) resistant staphylococci in the intestine (3) pseudomembranous colitis due to an overgrowth of clostridium difficile
- Benign intracranial hypertension (pseudotumor cerebri)
- Vestibular problems: e.g. dizziness, nausea, vomiting occur with minocycline, which concentrates in the endolymph of the ear and affects the function

CHLORAMPHENICOL

Broad-spectrum antibiotic active against a wide range of gram positive and gram negative organisms, anaerobes, and some intracellular bacteria e.g. rickettsiae

Does not affect P. aeruginosa and chlamydiae

Use is restricted to life-threatening infections because of its toxicity

Mostly bacteriostatic but bactericidal to H. influenza

Indications: Serious life-threatening infections such as H. influenzae, Bacteroides fragilis and meningitis when beta-lactams cannot be used or no other appropriate antibiotic is available, and in typhoid fever

CHLORAMPHENICOL …. CONT'D

Mechanism of action

- Binds to the bacterial 50S ribosomal subunit to block the action of peptidyl transferase and thus prevents amino acid incorporation into newly formed peptides
- Its toxicity is due to the similarity of mammalian mitochondrial ribosomes to those of bacteria. Protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels and bone marrow toxicity occurs.

Resistance

Results from the production of a plasmid encoded acetyltransferase which inactivates the drug

CHLORAMPHENICOL: PHARMACOKINETICS

- Administered intravenously or orally. It is completely absorbed after the oral route.
- Widely distributed including the CSF (it readily enters the CSF even with normal meninges)
- Primary route of elimination is by metabolism - glucuronidation in the liver. The glucuronide is then excreted renally
- Only about 10% of the parent compound is excreted by glomerular filtration
- It inhibits the hepatic mixed-function oxidases (cytochrome P450 enzymes)
- It is secreted into breast milk

CHLORAMPHENICOL: ADVERSE EFFECTS

- Hemolytic anemia - in patients with low levels of glucose 6-phosphate dehydrogenase
- Reversible anemia - dose-related and occurs concomitantly with therapy
- Aplastic anemia (pancytopenia): idiosyncratic and usually fatal; is independent of dose and may occur after therapy has ceased
- Potential teratogenic effects
- GIT: GIT disturbances, diarrhea (due to alteration of gut flora), hypovitaminosis B and K

CHLORAMPHENICOL: ADVERSE EFFECTS (CONT'D)

Gray baby syndrome

- Occurs in neonates due to low capacity to glucuronate chloramphenicol in neonates. The drug accumulates to levels that interfere with the function of mitochondrial ribosomes. Clinical features eatures include poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby") and death.
- Adults who have received very high doses may also exhibit this toxicity

Interactions

Inhibits some hepatic cytochrome P450 enzymes and blocks the metabolism of some drugs (e.g. warfarin, phenytoin, tolbutamide)

MACROLIDES

- Include erythromycin, roxithromycin, azithromycin, clarithromycin, telithromycin and spiramicin
- MOA: Bind irreversibly to a 50S subunit of the bacterial ribosome and inhibit the translocation step of protein synthesis. Are bacteriostatic.
- Are broad spectrum antibiotics

ERYTHROMYCIN

- Few indications where it is a drug of first choice
- Mostly used as an alternative to penicillin in allergy to beta-lactam antibiotics (especially gram positive bacteria, spirochaetes and N.gonorrhoae)
- Also used for Chlamydia, Mycoplasma, Legionella, Corynebacterium diphtheriae, vibrio cholerae and staphylococcus aureus (not MRSA)

CLARITHROMYCIN

- Similar to erythromycin, but it is also effective against H. influenzae
- Has higher activity than erythromycin against intracellular pathogens (e.g. Chlamydia, Legionella, Moraxella, Ureaplasma species) and H.pylori
- Is active against atypical mycobacteria and mycobacteria lepra

AZITHROMYCIN AND TELITHROMYCIN

Azithromycin

- Less active against streptococci and staphylococci than erythromycin
- More active against respiratory infections due to H. influenzae and Moraxella catarrhalis
- The preferred therapy for urethritis caused by Chlamydia trachomatis
- Has some activity against atypical mycobacteria

Telithromycin

Spectrum similar to azithromycin, and less vulnerable to resistance

MACROLIDES: BACTERIAL RESISTANCE

- Resistance to erythromycin is a serious clinical problem
- Most strains of staphylococci in hospital isolates are resistant to erythromycin
- Clarithromycin and azithromycin show cross-resistance with erythromycin
- Telithromycin can be effective against macrolide-resistant organisms

MACROLIDES: BACTERIAL RESISTANCE …. CONT'D

Mechanisms are involved include:

- Inability of the organism to take up the antibiotic or the presence of an efflux pump that limits the amount of intracellular drug
- A decreased affinity of the 50s ribosomal subunit for the drug
- Plasmid-associated erythromycin esterase that destroys the drug

MACROLIDES: ADMINISTRATION

- Absorbed orally
- Azithromycin available for IV infusion
- IV erythromycin - high incidence of thrombophlebitis, intramuscular injections are painful
- Food interferes with absorption of erythromycin and azithromycin but can increase that of clarithromycin

MACROLIDES: DISTRIBUTION

- Distributed well in all body fluids except the CSF
- Erythromycin is one of the few antibiotics that diffuses into prostatic fluids
- Inflammation allows for greater tissue penetration

MACROLIDES: ELIMINATION

Metabolism

- Are extensively metabolized with exception of azithromycin
- Inhibit enzymes of the CYP-450 system

Excretion

- Erythromycin and azithromycin: concentrated and excreted in an active form in the bile. Partial reabsorption occurs via enterohepatic circulation. Inactive metabolites are excreted into the urine.
- Clarithromycin and its metabolites are eliminated by the kidney as well as the liver (adjust dosage in compromised renal function)

MACROLIDES: ADVERSE EFFECTS

- Epigastric distress: common - it can lead to poor compliance for erythromycin. Clarithromycin and azithromycin - better tolerated by the patient, but GIT problems are also most common side effects.
- Cholestatic jaundice: especially with the estolate form of erythromycin, presumably as the result of a hypersensitivity reaction
- Ototoxicity: transient deafness with erythromycin, especially at high dosages
- Telithromycin – hepatotoxicity, prolongation of QTc interval, and may worsen myastenia gravis

MACROLIDES: DRUG INTERACTIONS

- Erythromycin, telithromycin, and clarithromycin inhibit the hepatic metabolism of a number of drugs (e.g. theophylline, warfarin, carbamazepine, cyclosporine and statins)
- Interaction with digoxin may occur in some patients – the macrolides eliminate a species of intestinal flora that ordinarily inactivates digoxin – thus bioavailability increases resulting in higher plasma concentration

CLINDAMYCIN

- Mechanism of action: as macrolides (antagonism occurs when co-administered)
- Used in the treatment of infections caused by anaerobic bacteria (e.g. Bacteroides fragilis). Also active against non-enterococcal gram-positive cocci (note: Clostridium difficile is resistant to clindamycin)
- Administered orally (well absorbed) or parenterally
- Distributes well into all body fluids except the CSF

CLINDAMYCIN …. CONT'D

- Penetration into bone occurs even in the absence of inflammation
- Metabolised in the liver and also excreted into the bile and urine (by glomerular filtration)
- Accumulation can occur in patients with either severely compromised renal function or hepatic failure

CLINDAMYCIN: ADVERSE EFFECTS

- Skin rashes
- GIT disturbances
- Impaired liver function
- The most serious adverse effect is potentially fatal pseudomembranous colitis (caused by overgrowth of Clostridium difficile; can be treated with vancomycin)

LINEZOLID

Mechanism of action

Inhibits of bacterial protein synthesis - blocks the formation of the 70s initiation complex by binding to 50s subunit. It is bacteriostatic.

Anti-bacterial spectrum

Linezolid is active against resistant gram positive organisms (e.g., methicillin- and vancomycin-resistant S. aureus, vancomycin-resistant Enterococcus faecium and Enterococcus faecalis, and penicillin-resistant streptococci) and mycobacterium tuberculosis

LINEZOLID

- Resistance: occurs due to decreased binding to the target site. Cross-resistance with other antibiotics does not occur.
- Indications: Staphylococcus osteomyelitis, MRSA and VRE, multidrug resistant S. pneumoniae, and second-line treatment of tuberculosis
- Adverse effects: Myelosuppression, pseudo-membraneous colitis

AMINOGLYCOSIDES, FOLATE ANTAGONISTS, METRONIDAZOLE, RIFAMPICIN, STREPTOGRAMINS & FUSIDIC ACID

AMINOGLYCOSIDES

Include amikacin, gentamicin, tobramycin, streptomycin, neomycin, netilmicin and kanamycin

Mechanism of action

- Inhibit bacterial protein synthesis through binding to the 30S ribosomal subunit
- Are bactericidal
- Susceptible organisms have an oxygen-dependent system that transports the drug across the cell membrane
- Active only against aerobic bacteria (anaerobes lack the oxygen-requiring transport system)

AMINOGLYCOSIDES: BACTERIAL RESISTANCE

Bacterial resistance to aminoglycosides ccurs rapidly by the following three mechanisms:

1. Decreased uptake: The oxygen-dependent transport system for aminoglycosides or porins are absent
2. Altered binding site: The 30s ribosomal subunit binding site has a lowered affinity for aminoglycosides
3. Enzymatic modification: Important mechanism; plasmid-associated (synthesis of e.g. acetyltransferases, nucleotidyltransferases, and phosphotransferases – there are nine or more of these enzymes) modify and inactivate aminoglycosides (netilmicin and amikacin are less vulnerable to these enzymes than other aminoglycosides)

AMINOGLYCOSIDES: CLINICAL USES

1. Serious infections due to aerobic gram-negative bacilli (use is limited by the occurrence of serious toxicities)
2. Streptomycin, amikacin and kanamycin can be used to treat tuberculosis
3. Tularemia

NB: Aminoglycosides are synergistic with beta-lactam anti-bacterial drugs and vancomycin, which enhance diffusion of aminoglycosides into the cell

AMINOGLYCOSIDES: PHARMACOKINETICS

- Aminoglycosides are not absorbed orally – thus must be given parenterally to achieve adequate serum levels (however neomycin is given orally to reduce flora in the gut in hepatic failure – too toxic for parenteral use)
- Extracellular distribution
- Does not enter cerebrospinal fluid (penetration is poor even when the meninges are inflamed). Except for neomycin, they may be administered intrathecally.
- All aminoglycosides are rapidly excreted into the urine predominantly by glomerular filtration
- Accumulation occurs in patients with renal failure and dose adjustment is required

AMINOGLYCOSIDES: ADVERSE EFFECTS

Patient factors that predispose to aminoglycoside toxicity

- Age, renal function, sepsis (the elderly are particularly susceptible to nephrotoxicity and ototoxicity)
- Previous exposure to aminoglycosides
- Functional acummulation

Therapeutic drug monitoring through measuring plasma levels is important with aminoglycosides

AMINOGLYCOSIDES: ADVERSE EFFECTS

Nephrotoxicity and otoxicity

- Aminoglycosides accumulate in the renal cortex, and in the endolymph and perilymph of the inner ear
- Nephrotoxicity and ototoxicity are directly related to high peak plasma levels and the duration of treatment

AMINOGLYCOSIDES: ADVERSE EFFECTS (CONT'D)

Ototoxicity

- Deafness may be irreversible and can affect fetuses in utero
- Vertigo and loss of balance: especially in patients receiving streptomycin
- Patients simultaneously receiving other ototoxic drug (e.g., diuretics frusemide, bumetanide and ethacrynic acid, vancomycin and cisplatin) are particularly at risk

Nephrotoxicity

Retention of the aminoglycosides by the proximal tubular cells results in kidney damage (from mild, reversible impairment to severe, acute tubular necrosis, which can be irreversible)

AMINOGLYCOSIDES: ADVERSE EFFECTS (CONT'D)

Neuromuscular paralysis

- Mostly after direct intraperitoneal or intrapleural application of large doses
- They inhibit the release of acetylcholine from presynaptic nerve endings and reduce the sensitivity of the postsynaptic sites to acetylcholine
- Patients with myasthenia gravis are particularly at risk
- Prompt administration of calcium or neostigmine can reverse the block

AMINOGLYCOSIDES: ADVERSE EFFECTS (CONT'D)

Allergic reactions

Contact dermatitis - a common reaction to topically applied neomycin

Teratogenic

All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid

SELECTED AMINOGLYCOSIDES AND THEIR CLINICAL USES

- Gentamicin and tobramycin: enterobacter, proteus, pseudomonas, klebsiella and serratia species and other gram negative bacteria. They are often used in combination with beta-lactam antibiotics for serious infections that require broad coverage
- Amikacin: severe gram negative infections (especially those resistant to gentamicin and tobramycin) and in second-line regimens for tuberculosis

SELECTED AMINOGLYCOSIDES AND THEIR CLINICAL USES …. CONT'D

- Streptomycin: plague, brucellosis, tuberculosis
- Neomycin and kanamycin: administered topically for minor soft-tissue infections (especially in combination with bacitracin and polymixin). Neomycin is also used orally for hepatic encephalopathy. Kanamycin is also used in second-line regimens for tuberculosis.

SPECTINOMYCIN

- Structurally related to aminoglycosides
- Inhibits the 30S ribosomal subunit thus inhibits protein synthesis
- Used only for treatment of acute gonorrhea caused by penicillinase-producing Neisseria gonorrhea and/or uncomplicated gonorrhea of the genitalia or rectum, in patients who are allergic to penicillins
- Administered as a single IM injection
- Hypersensitivity reactions can develop

FOLIC ACID ANTAGONISTS

- Coenzymes containing folic acid are required for the synthesis of purines and pyrimidines, and other compounds necessary for cellular growth and replication
- In the absence of folic acid, bacteria cannot grow or divide
- Humans cannot synthesize folic acid and thus obtain preformed folate as a vitamin from the diet
- Many bacteria are impermeable to folic acid, and must synthesize folate de novo

FOLIC ACID ANTAGONISTS

Mechanisms by which folic acid antagonists act

- Inhibit the synthesis of folic acid by inhibiting the enzyme dihydropteroate synthetase (e.g. sulfonamides) which is required for the synthesis of dihydrofolate from para-aminobenzoic acid (PABA)
- Prevent the conversion of folic acid to its active, coenzyme form (tetrahydrofolic acid) (e.g. trimethoprim) [the enzyme involved is dihydrofolate reductase]

SULFONAMIDES

- Structurally related to p-aminobenzoic acid (PABA) the substrate of the enzyme dihydropteroate synthetase
- Are bacteriostatic
- Spectrum: Active against selected enterobacteriaceae, chlamydia and nocardia
- Because of the development of resistance and availability of better antimicrobials, sulfonamides are no longer widely used

SULFONAMIDES

- Sulfadiazine and sulfadoxine have some activity against some protozoa (toxoplasma gondii and plasmodia species). They are used in combination with the dihydrofolate reductase inhibitor, pyrimethamine, in the treatment for toxoplasmosis and P. falciparum malaria respectively.
- Resistance: bacteria acquire resistance to sulfonamides by (1) mutations resulting in overproduction of PABA (2) using alternative metabolic pathway for folic acid synthesis (3) developing low permeability to sulfonamides. Cross resistance occurs among the sulfonamides.

SULFONAMIDES: PHARMACOKINETICS

- Well absorbed after oral administration (except for sulfasalazine which is not absorbed and is used in the treatment of chronic inflammatory bowel disease (intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate which have anti-inflammatory effect)
- Sulfonamides are rarely given IV - reserved for patients who are unable to take them orally
- Due to risk of sensitization, sulfonamides are not usually applied topically (except silver sulfadiazine which is applied topically to reduce burns associated sepsis)

SULFONAMIDES: PHARMACOKINETICS …. CONT'D

- Bind extensively to serum albumin
- Widely distributed to all body tissues with good penetration into CSF (even without meningeal inflammation)
- They can pass the placental barrier
- Metabolism: Acetylated in the liver and the metabolite retains the potential to precipitate in the kidney at neutral or acidic pH (crystalluria) with potential damage to the kidney
- Excretion: by glomerular filtration (both parent drug and metabolites) - depressed kidney function results in accumulation of both the parent compounds and metabolite

EXAMPLES OF SULFONAMIDES USED CLINICALLY

- Well absorbed orally, short-acting: sulfadiazine, sulfadimidine, sulfisoxazole
- Well absorbed, intermediate acting: sulfamethoxazole
- Well absorbed orally, long-acting: sulfadoxine (used in the management of malaria)
- Poorly absorbed in GIT: sulfasalazine (sulfapyridine)
- Used topically: silver sulfadiazine, sulfacetamide

SULFONAMIDES USED FOR SPECIFIC PURPOSES

- Sulfacetamide: sodium salt is water-soluble and is used in eye-drops for bacterial eye infections
- Silver sulfadiazine: used topically for management of burn wounds
- Sulfasalazine: treatment of inflammatory bowel disease
- Sulfadoxine: extra long acting sulfonamide. Useful for treatment of P. falciparum malaria

SULFONAMIDES: CLINICAL USES

- Urinary tract infections – sulfadimidine, sulfisoxazole, co-trimoxazole (sulfamethoxazole-trimethoprim)
- Nocardiosis (high doses) – co-trimoxazole
- Toxoplasmosis (sulfadiazine in combination with pyrimethamine)
- Trachoma (as alternatives to tetracyclines which are the drugs of choice) – sulfacetamide, co-trimoxazole

SULFONAMIDES: CLINICAL USES …. CONT'D

- Lymphogranuloma venereum and chancroid (as alternatives to tetracyclines) – co-trimoxazole
- Malaria (sulfadoxine in combination with pyrimethamine)
- Bacterial conjunctivitis (sulfacetamide)
- Ulcerative colitis (sulfasalazine)

SULFONAMIDES: ADVERSE EFFECTS

- Nephrotoxicity: a result of crystalluria (from both the parent compound and the metabolites) – can be prevented by adequate fluid intake and urine alkalinization (sulfisoxazole and sulfamethoxazole are more soluble at urinary pH than the older sulfonamides and are therefore less likely to cause nephrotoxicity)
- Hypersensitivity: common adverse effect (rashes, fever, angioedema, anaphylactoid reactions, Stevens-Johnson syndrome, hepatitis) - more frequently with the longer-acting agents

SULFONAMIDES: ADVERSE EFFECTS …. CONT'D

- Hemopoietic disturbances: hemolytic anemia in patients with glucose 6-phosphate dehydrogenase deficiency, granulocytopenia and thrombocytopenia can also occur
- Nausea, vomiting, headache, mental depression
- Kernicterus: occurs in neonates due to the displacement of bilirubin from its binding sites on albumin and its penetration into CNS (the neonate's blood-brain barrier is not fully developed)

SULFONAMIDES: DRUG INTERACTIONS

Sulfonamides displace some drugs from serum albumin e.g. sulfonylureas, warfarin and methotrexate

DIHYDROFOLATE REDUCTASE INHIBITORS: TRIMETHOPRIM

- MOA: inhibits bacterial dihydrofolate reductase
- It is bacteriostatic
- Antibacterial spectrum similar to sulfonamides
- May be used alone in the treatment of acute UTIs, and in the treatment of bacterial prostatitis and vaginitis
- Is relatively selective to bacterial dihydrofolate reductase and thus has low toxicity
- Mostly used in combination with sulfamethoxazole (the combination is called co-trimoxazole)

TRIMETHOPRIM: PHARMACOKINETICS

- It is a weak base and attains high concentrations in relatively acidic prostatic and vaginal fluids
- Well absorbed orally
- It also penetrates the CSF
- Mostly excreted unchanged through the kidney

TRIMETHOPRIM: ADVERSE EFFECTS

- Folic acid deficiency: megaloblastic anemia, leukopenia, granulocytopenia, seen especially in pregnant women and patients with a poor diets. These blood disorders can be reversed by the simultaneous administration of folinic acid (tetrahydrofolic acid), which does not enter bacteria
- Nausea, vomiting, skin rashes

CO-TRIMOXAZOLE

- Co-trimoxazole is a combination of trimethoprim and sulfamethoxazole
- The ratio of trimethoprim:sulfamethoxazole is 1:5 to attain the optimum plasma concentration
- MOA: Sequential blockade in the synthesis of tetrahydrofolic acid - sulfamethoxazole inhibits synthesis of dihydrofolate from PABA, while trimethoprim inhibits conversion of dihydrofolate to tetrahydrofolate
- The combination of trimethoprim with sulfamethoxazole is synergistic (reduction in MIC of each drug and extension of antimicrobial spectrum) and bactericidal

CO-TRIMOXAZOLE …. CONT'D

- Active against several gram positive and gram negative bacteria
- Susceptible organisms include: meningococci, gonococci, E.coli, Yersinia, Shigella, Salmonella, C. diphtheriae, H. influenzae, Staphylococcus aureas (including methicillin resistant organisms), streptococci and Pneumocystis jirovecii
- Development of resistance to the combination is slower when compared to either drugs given alone

CO-TRIMOXAZOLE: CLINICAL INDICATIONS

- Urinary tract infections: (1) uncomplicated infection of the lower urinary tract infection (2) chronic and recurrent urinary tract infections (including enterobacteriaceae)
- Bacterial prostatitis and bacterial vaginitis
- Respiratory tract infections: including bronchitis, sinusitis and otitis media
- Drug of choice for pneumocystis jiroveci pneumonia (prophylaxis and treatment)

CO-TRIMOXAZOLE: CLINICAL INDICATIONS …. CONT'D

- Gastroenteritis due to Shigella and E.coli
- Ampicillin- or chloramphenicol-resistant systemic salmonella infections
- Chancroid (co-trimoxazole is the drug of choice)

Co-trimoxazole is most commonly given orally (given IV in patients unable to take oral)

CO-TRIMOXAZOLE: ADVERSE EFFECTS

- Hypersensitivity reactions: the hypersensitivity reactions caused by sulfamethoxazole occur (they are not dose-dependent). Reactions involving the skin are very common.
- Drug-induced fever
- GIT: nausea, vomiting, glossitis, stomatitis and diarrhoea
- Hemolytic anemia: in patients with glucose 6-phosphate dehydrogenase deficiency due to the sulfamethoxazole

CO-TRIMOXAZOLE: ADVERSE EFFECTS…. CONT'D

- Hematological: Megaloblastic anemia, leukopenia, thrombocytopenia may be reversed by administration of folinic acid (folinic acid does not enter the microorganism)

NB: Patients with AIDS are more prone to the adverse effects of co-trimoxazole

METRONIDAZOLE

- MOA: Inhibition of DNA replication in anaerobic organisms
- Spectrum: Bactericidal against most anaerobic bacteria, clostridium difficile and anaerobic protozoa (e.g. Trichomonas vaginalis and Entamoeba histolytica)
- Pharmacokinetics: Excellent oral absorption, penetrate bones teeth, CNS abscesses/CSF, crosses the placenta and enters milk. Metabolized in liver.
- Indications: Infections caused by Bacteroides fragilis, anaerobes in abdominal and pelvic cavity, diarrhea by C. difficile, cerebral abscesses, trichomonas infections, tetanus, H. pylori

METRONIDAZOLE …. CONT'D

- Adverse effects: Metallic taste, GIT disturbances, dizzines, vertigo , headache, depression, dark urine, inhibits acetaldehyde dehydrogenase and can thus cause serious toxicity when taken with ethanol
- Contraindicated in the first trimester of pregnancy
- Tinidazole: Similar to metronidazole but has a longer duration of action

RIFAMPICIN

- Broad spectrum antibiotic: gram positive and gram negative bacteria, meningococci, H. influenzae, and mycobacteria (tuberculosis, leprosy and atypical mycobacteria)
- Drugs in the same class (rifamycins) include rifabutin and rifapentin
- MOA: blocks bacterial DNA-dependent RNA polymerase - inhibits RNA synthesis. It is bactericidal.
- Indications: Tuberculosis, leprosy, atypical mycobacteria infections, prophylaxis of H.influenzae and meningococcal meningitis, resistant staphylococcal infections, brucellosis, and to eradicate carrier state of meningococcus, H.influenzae and S. aureus

RIFAMPICIN: PHARMACOKINETICS

- Well absorbed orally
- Widely distributed in all body tissues and fluids, with adequate levels in CSF even in the absence of inflammation
- Metabolized in the liver and undergoes enterohepatic circulation
- Induces activity of hepatic cytochrome P450 enzymes
- Elimination: Rifampicin and its metabolites are eliminated via the bile into faeces and via urine

RIFAMPICIN: ADVERSE EFFECTS

- GIT disturbances: nausea, vomiting, abdominal cramps, diarrhoea
- Hypersensitivity reactions: rash, urticaria, fever, nephritis, haemolysis
- Hepatotoxicity
- CNS: headache, drowsiness, dizziness, ataxia, confusion and peripheral neuropathy

RIFAMPICIN: DRUG INTERACTIONS

Induces cytochrome P450 enzymes: this can increase the clearance of co-administered drugs (e.g. clofibrate, digoxin, ketoconazole, sulfonylureas, warfarin, oral contraceptives, corticosteroids, quinidine)

STREPTOGRAMINS: QUINUPRISTIN/DALFOPRISTIN

- A combination of two streptogramin antibiotics, quinupristin and dalfopristin, which are combined in a weight-to-weight ratio of 30% quinupristin to 70% dalfopristin
- MOA: Each component binds to a separate site on the 50s bacterial ribosome, forming a stable complex. They synergistically interrupt protein synthesis. The mixture is bactericidal.
- Reserved for vancomycin-resistant enterococcus faecium (VRE) and gram positive cocci (staphylococci)

QUINUPRISTIN/DALFOPRISTIN …. CONT'D

- Administered IV in 5% dextrose solution (incompatible with saline)
- They penetrate macrophages and polymorphonucleocytes (important because VRE are intracellular)
- Levels in the CSF are low

QUINUPRISTIN/DALFOPRISTIN: ADVERSE EFFECTS

- Venous irritation: common when administered through a peripheral line
- Arthralgia, myalgia: when higher doses of the drugs are employed
- Hyperbilirubinemia: total bilirubin is elevated in about 25% of patients, resulting from a competition with bilirubin for excretion

QUINUPRISTIN/DALFOPRISTIN: DRUG INTERACTIONS

- Ability of quinupristin/dalfopristin to inhibit CYP3A4 isozyme - concomitant administration with drugs metabolized by this pathway may lead to toxicities
- Interaction with digoxin – eradicates the gut bacteria which degrade digoxin, thereby increasing digoxin bioavailability

FUSIDIC ACID

- A narrow spectrum steroid antibiotic – active only against staphylococci
- MOA: Inhibits binding of tRNA to the ribosome thereby inhibiting protein synthesis
- Well absorbed orally, does not cross CSF, concentrates in bones. Also given IV.
- Used mainly in penicillin-resistant staphylococcal infections (in combination with another anti-staphylococcal effective agent)
- Adverse effects: GIT disturbances, skin eruption, jaundice

URINARY TRACT ANTI-SEPTICS AND TOPICAL ANTI-BACTERIAL AGENTS

URINARY TRACT ANTISEPTICS

- About 80% of UTIs are caused by E. Coli. The rest are caused by Staphylococcus saprophyticus, Klebsiella pneumoniae and Proteus mirabilis
- Urinary antiseptics are those anti-bacterial agents which are concentrated in urine but do not achieve systemic antibacterial concentrations. Their use is restricted to treatment of UTIs.
- Some anti-bacterial agents treatment of UTIs are known as urinary antiseptics
- They include methenamine, nalidixic acid, norfloxacin and nitrofurantoin

METHENAMINE

- MOA: Releases formaldehyde in acidic urine below pH 5.5. Formaldehyde is bactericidal to most bacteria and resistance does not develop to it. Urea-splitting bacteria that alkalinize the urine (e.g. proteus) are usually resistant to methenamine.
- Indication: Chronic UTI that is resistant to other drugs
- Given orally
- It is antagonistic to sulfonamides; binds sulfonamides and neutralises their action
- Adverse effects: High doses can cause nausea, epigastric distress, haematuria and painful micturition

NITROFURANTOIN

- MOA: Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA
- Narrow spectrum and bacteriostatic
- Active against E. coli (other common urinary tract gram negative bacteria are resistant) and gram positive cocci
- Activity is greater in acidic urine

NITROFURANTOIN …. CONT'D

- Complete absorption after oral absorption
- Rapidly excreted by glomerular filtration
- Adverse effects: GIT disturbances frequent (nausea, vomiting and diarrhea – reduced by administration with food), acute pneumonitis and interstitial pulmonary fibrosis, neurological problems (headache, nystagmus and polyneuropathies), hemolytic anemia (in patients with glucose-6-phosphate dehydrogenase deficiency) and hypersensitivity reactions

NALIDIXIC ACID AND NORFLOXACIN

- Nalidixic acid is a quinolone while norfloxacin is a flouroquinolone
- MOA: Inhibit DNA gyrase (topoisomerase II) thereby inhibiting replication of bacterial DNA
- Are active against most of the gram negative bacteria causing that cause UTIs (most gram positive organisms are resistant)
- Plasma levels of free nalidixic acid and norfloxacin are insufficient for treatment of systemic infections (the concentration of nalidixic acid achieved in the urine is 10-20 times greater than that in the plasma)

NALIDIXIC ACID AND NORFLOXACIN …. CONT'D

Adverse effects

- Mostly nausea, vomiting, and abdominal pain
- Urticaria, photosensitivity
- Liver function may be affected if therapy lasts longer than 2 weeks
- CNS: headache, malaise and visual disturbances (rare)

TOPICAL ANTI-BACTERIAL AGENTS

Polymyxin B and colistin (polymyxin E)

- Basic polypeptides that act to disrupt cell membrane functions
- Bactericidal and active against gram negative bacteria (pseudomonas, coliforms)
- Not absorbed from GIT
- Adverse effect: Neurotoxicity and nephrotoxicity
- Indications: Gut sterilisation (given orally), eye, ear and skin infections (topical application) and pseudomonas aeruginosa infection in cystic fibrosis (by inhalation)

TOPICAL ANTI-BACTERIAL AGENTS …. CONT'D

Bacitracin

- A mixture of polypeptides that acts by inhibiting bacterial cell wall synthesis
- Spectrum: Gram-positive organisms
- Use is restricted to topical application because of its nephrotoxicity

TOPICAL ANTI-BACTERIAL AGENTS …. CONT'D

Mupirocin

- Rapidly inactivated after absorption (thus very low systemic concentrations)
- Narrow spectrum anti-bacterial agent: Active against staphylococci including methicillin-resistant S. aureus (more than 95% of hospital staphylococcal isolates are still susceptible)
- MOA: Inhibits staphylococcal isoleucyl tRNA synthetase
- Used as an ointment for topical treatment of minor skin infections (e.g. impetigo)

END

Thanks for listening