ANTIBIOTICS

SOME GENERAL PRINCIPLES

- Antibiotics can be naturally produced, semi-synthetic, or synthetic substances
- Designed to have as much selective toxicity on the bacteria as possible
- This is more likely to be achieved compared to antimicrobials acting against eukaryotic cells (fungi, protozoa)

EXAMPLES OF SELECTIVE ACTION

- Penicillin on bacterial cell wall (organisms without cell wall won't be inhibited eg Mycoplasma pneumoniae)
- Sulphonamides prevent bacteria synthesising folic acid whereas humans can use preformed folate
- Generally drugs acting on cell membranes or protein synthesis are more toxic to humans

ANTIBIOTICS ACTING ON CELL WALL OF BACTERIA

- Beta lactams:
- Penicillins, cephalosporins, carbapenems, monobactam

- Glycopeptides:
- Vancomycin, teicoplanin

THE IDEAL ANTIBIOTIC?:PENICILLIN

- Narrow spectrum
- Bactericidal
- Very selective mode of action
- Low serum protein binding
- Widely distributed in body esp. CNS
- Excreted by the kidneys

THE DEVELOPMENT OF THE BETA LACTAMS

- Benzylenicillin and early cephalosporins mainly active against gram positive bacteria

  (strep and staph)
- Then “broad spectrum” penicillins appeared: ampicillin, ureidopenicillins and cephalosporins: cefuroxime, cefotaxime
- Carbapenems and latest generation of cephalosporins, eg ceftazidime more active against gram negatives

BENZYLPENICILLIN: MAIN INDICATIONS

- *Strep pyogenes* sepsis (from sore throat to fasciitis)
- Pneumococcal pneumonia, meningitis
- Meningococcal meningitis, sepsis
- Infective endocarditis (strep)
- Strep group B sepsis
- Diphtheria
- Syphilis, leptospirosis

Broader spectrum penicillins

- Ampicillin, amoxycillin cover most organisms hit by penicillin but also *Esch coli,* some *Proteus* (cause UTI's)
- Augmentin stable to TEM1 beta lactamase because of the clavulanic acid therefore more active than ampicillin
- Tazocin: broader coverage than augmentin against gram negatives including *Pseudomonas*

Organisms producing TEM1beta lactamase

- *Haemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Bacteroides fragilis*
- *Staph aureus*
- *Esch coli*

Carbapenems

- Imipenem, meropenem: have a very broad spectrum activity against gram-negative bacteria, anaerobes, streps
- Now used to treat gram negative infections due to so called ESBL producing organisms eg, *E coli, Klebsiella*
- Ertapenem is a new member of the group but its not active against Pseudomonas

PENICILLIN IS GENERALLY VERY SAFE BUT….

- Allergic reactions not uncommon-rashes
- Most severe reaction being anaphylaxis
- A history of anaphylaxis, urticaria, or rash immediately after penicillin indicates risk of immediate hypersensitivity after a further dose of any penicillin or cephalosporin (therefore these must be avoided)
- Allergy is not dependent on the dose given ie, a small dose could cause anaphylaxis
- Very high doses of penicillin can cause neurotoxicity
- Never give penicillin intrathecally

What antibiotics can be used in penicillin allergy?

- Macrolides: erythromycin, clarithromycin
- (mainly gram positive cover)
- Quinolones: ciprofloxacin, levofloxacin (mainly gram positive cover)
- Glycopeptides (serious infections)
- Fusidic acid, rifampicin, clindamycin (mainly gram positive)

REMEMBER WHAT THE OTHER BETA LACTAMS ARE:

- All penicillins: ampicillin, augmentin, piperacillin, cloxacillin
- Cephalosporins: cefuroxime, cefotaxime, ceftriaxone, ceftazidime (5-10% cross sensitivity)
- Monobactam: aztreonam (low cross sensitivity)
- Carbapenems: imipenem, meropenem

CLOXACILLIN

- Narrow spectrum: *Staph aureus* (MSSA)
- Stable to TEM1 beta lactamase
- Similar antibiotics are methicillin, nafcillin
- Similar safety profile to benzylpenicillin
- MRSA emerged in the early 1970's (*MecA* gene encoding additional pbp)

Cephalosporins: main uses

- Cefuroxime: surgical prophylaxis
- Cefotaxime/ceftriaxone: meningitis nosocomial infections excluding Pseudomonal,
- Ceftazidime: nosocomial infections including Pseudomonal

Problems with antibiotic resistance: how does it happen?

- Some bacteria are naturally resistant to particular antibiotics (*Pseudomonas* has permeability barrier to many antibiotics)
- Some typically susceptible species have minority populations which are resistant by virtue of mutational resistance (pneumococcus)
- Other species acquire resistance via plasmids ("infectious resistance") eg *Neisseria gonorrhoeae,* many gram negatives

Current major antibiotic resistance problems: community infections

- Respiratory tract: penicillin resistance in pneumococcus (5-10%)
- Gastrointestinal: quinolone resistance in Campylobacter
- Sexually transmitted: penicillin, quinolone resistance in gonococcus
- Urinary tract: beta lactam resistance in *Esch coli*
- MRSA and MDRTB
- Tropical: multidrug resistance in *Salmonella typhi, Shigella spp*

Current major resistance problems: hospital infections

- MRSA: current strains are often multiply-antibiotic resistant
- VISA/GISA: intermediate resistance to glycopeptides (thickened cell wall)
- VRSA/GRSA: highly resistant (transferable on plasmids) from enterococci
- VRE: enterococci (multiply resis tant)
- Broad spectrum beta lactam resistant (ESBL) *Esch coli, Klebsiella*
- Multiply antibiotic resistant enterobacteria: *Acinetobacter, Stenotrophomonas, Serratia*

Other major antibiotic groups: aminoglycosides

- Gentamicin, amikacin (tobramycin, streptomycin)
- Mainly active against gram negative bacteria
- Mainly used to treat nosocomial infections: pneumonia in ITU, septicaemia
- Limiting factors are nephrotoxicity (and ototoxicity) and resistance
- Also used in combination

How we give aminoglycosides

- For serious nosocomial infections: “extended interval” or once daily dosing
- 5 or 7mg/kg for gentamicin (Hartford nomogram)
- Rationale based on concentration-dependent killing and post-antibiotic effect
- Reduced risk of nephrotoxicity
- In infective endocarditis use lower doses to give synergy with penicillin

Some indications and limitations of particular antibiotics

Community acquired pneumonia

- Pneumococcus (and *H influenzae*) are most likely: therefore ampicillin, amoxycillin or augmentin
- Severe pneumonia: cefotaxime
- Severe atypical pneumonia (*Legionella*): macrolide or quinolone
- Resistant pneumococcus: vancomycin or linezolid (new antibiotic!)
- A new quinolone moxifloxacin covers most of these pathogens (likely to be used more in community)

Community acquired urinary infections

- Ampicillin, amoxycillin, augmentin
- Oral cephalosporin: cephradine
- Trimethroprim
- Nalidixic acid
- Nitrofurantoin
- Ciprofloxacin
- Mecillinam

Skin and soft tissue infections

- Cellulitis ? Streptococcal: penicillin or augmentin
- Infected eczema ? Staphylococccal/mixed: penicillin+flucloxacillin or augmentin
- Necrotising fasciitis: penicillin+clindamycin
- Septic arthritis: fluclox+fusidic acid
- Gangrene: metronidazole

Where there is deep-seated infection: bone, abscess

- Need an antibiotic with good tissue and phagocyte penetration
- Examples are rifampicin, clindamycin, fusidic acid, ciprofloxacin, metronidazole
- So for treatment of Staph aureus osteomyelitis: flucloxacillin+ fusidic acid

Why do we use combination therapy?

- When treating serious infection empirically we want to cover a broad spectrum

(severe pneumonia:cefotaxime+erythromycin)

- To prevent the emergence of drug resistance: tuberculosis regimens
- For synergy: infective endocarditis (aminoglycoside)
- For mixed infections eg, abdominal sepsis (tazocin+metronidazole)

Factors to consider when prescribing an antibiotic

- Any history of allergy, toxicity?
- Is it appropriate for the spectrum I want to cover?
- What route of admin: oral or i.v?
- Any factors affecting absorption ?
- Is it going to reach the site of infection?
- Any drug interactions?
- Any serious toxicity eg, hepatic, renal?
- Does it need monitoring eg aminoglycosides, vancomycin, streptomycin?

Some other antibiotics occasionally used

- Co-trimoxazole (*Stenotrophomonas*)
- Chloramphenicol (typhoid fever, meningitis)
- Colistin (resistant *Pseudomonas*) topical
- Neomycin: gut decontamination, topical

Special situations

- Paediatrics
- Obesity
- Renal failure (haemodialysis/filtration)
- Hepatic failure
- CNS infections
- Epidemiology (contacts of cases