Primary Cast Episode 3 - Antimicrobial Pharmacology

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Tips for answering this topic!

- ***MOAs:*** *anything that acts on the cell wall is bacteriocidal, acts on the ribosome is bacteriostatic.*
- ***Answer PK questions using the format:*** *A/D/M/E, if you don't know the details, just offer up anything you know about dosing from your daily practice.*
- ***Remembering ribosome activity "buy AT 30, CELL at 50"***
    - *"AT 30" Aminoglycosides and Tetracyclines on the 30*
    - *"CELL 50" Chloramphenicol, Erythromycin (and other macrolides), Lincosamides (i.e. clindamycin) and Linezolid.*
    - *Sometimes is I am on the spot and asked about macrolides i imagine that "Macro = big so it must be the big one*

1. Penicillin

Describe the mechanism of action of penicillins

- Bacteriocidal
- Inhibition of bacterial cell wall synthesis
- Covalent binding to penicillin binding proteins
- Interfere with cross linking and formation of peptidoglycan

How does resistance to penicillins occur?

- Inactivation by beta-lactamase
- Modification of target penicillin binding proteins
- Impaired penetration of drug
- Efflux pumps

What is the microbial spectrum of penicillin G?

- Streptococci, meningococci, enterococci, some pneumococci
- Treponema pallidum
- Clostridia
- Non beta lactamase producing staph

What are the manifestations of penicillin allergy?

- Anaphylaxis
- Fever
- Skin pathology – rash, Steven Johnson Syndrome

What are some other side effects of penicillin?

- Renal failure
- Seizure at high doses
- GI disturbance
- Hepatitis

How are penicillins eliminated in the body?

- Renal excretion and active secretion
- Biliary secretion

How does probenecid alter the elimination of some penicillins?

- Inhibits secretion of weak acid from the proximal tubule.

What circumstances encourage the development of bacterial resistance to antimicrobial agents?

- Resistance is an example of natural selection and arises through spontaneous mutations or DNA exchange between bacteria.
- It is promoted by :
- Dirty hospital environments with multiple species of bacteria cp-existing and exchanging between hospital patients, the environment and staff.
- A course of antibiotics that only partially treats an infection - can result from both overuse and underuse of antibiotics.
- Total consumption of antibiotics in a human population os the critical factor in development of resistant strains.

2. Flucloxacillin

What is the MOA of flucloxacillin?

- Bacteriocidal, beta lactam antibiotic
- Inhibits bacterial cell growth by binding to the active site of penicillin binding proteins
- Interferes with cell wall synthesis which leads to cell death

What microorganisms are susceptible to flucloxacillin?

- Staphylococci (including beta lactamase producing) and streptococci.
- No activity against enterococci, anaerobes, gram negatives or MRSA.

What are the side effects of flucloxacillin?

- Allergy/anaphylaxis, GIT upset, cholestasis, interstitial nephritis, neutropaenia, serum sickness

What is the frequency of cross allergenicity between flucloxacillin and cephalosporins?

- 5-10%

Why is oral fluclox given before meals?

- It is inactivated by gastric acid and binds to food proteins which can decrease absorption

3. **Cephalosporins**

What is the MOA of cephalosporins?

- Bacteriocidal, beta lactam antibiotic
- Inhibit bacterial cell wall synthesis by halting peptidoglycan synthesis

How are they classified and give an example of each class

- 1st generation – cephalexin and cefazolin. Active against gram positive cocci. Not active against pseudomonas.
- 2nd generation – Added gram negative coverage. Cefuroxime, Cefaclor
- 3rd generation – Crosses BBB, more gram neg coverage. Ceftriaxone and Ceftazidime which works against Pseudomonas.
- 4th generation – Extended gram negative cover, more resistant to beta lactamase, pseudomonas cover, crosses BBB. Cefepime

Study Tip: *A great way to remember the names and their classifications can be found on this youtube video:* https://www.youtube.com/watch?v=djipSuNjqmw

Are there any CNS infections that cephalosporins do not cover?

- Listeria, resistant strains of pneumococci and e.coli

What are the adverse effects of cephalosporins?

- Hypersensitivity reaction similar to penicillin, 5-10% cross reactivity. Fever, skin rashes, neutropaenia, haemolytic anaemia. Can cause interstitial nephritis and ATN.

Can you Explain the microbial spectrum of activity of ceftriaxone?

- Not usual degraded by beta lactamases, so a broader spectrum of activity
- Expanded gram negative cover and crosses the blood brain barrier
- Active against neisseria and haemophilus
- Not active against pseudomonas

What is the clinical relevance of ceftriaxones half life?

- Half life is 7-8 hours so it may be administered once daily

4. **Vancomycin**

What is the mechanism of action of vancomycin?

- Bacteriocidal antibiotic.
- Inhibits cell wall synthesis by binding to peptidoglycan pentopeptide.
- Prevents cross linking of the wall, which leads to weakening of the wall and cell membrane

What are the target organisms of vancomycin

- Gram positive staph including MRSA and enterococci
- Gram positive anaerobes like clostridium difficile

Which clinical conditions require dose adjustment?

- Renal impairment and obesity

5. **Gentamicin**

What class of antibiotic is gentamicin?

- Aminoglycoside

What is its mechanism of action?

- Bacteriostatic.
- Acts by binding irreversibly to the 30s subunit of the bacterial ribosome, inhibiting protein synthesis in 3 ways;
- By interfering with the initiation complex of peptide formation
- Inducing misreading of mRNA to produce non functional proteins
- Causing the breakup of polysomes to non-functioning monosomes
- Exhibits concentration dependent killing and post antibiotic effect

Please describe the pharmacokinetics of gentamicin.

- A: IV, IM, inhalational or topical (poor PO absorption)
- D: Small volume of distribution, <10% protein bound, achieves high concentrations in renal cortex
- M: Not metabolised
- E: Renal dependent elimination, glomerular filtration. Half life 2-3 hours, given daily. Dose adjustment required for renal failure.

What microorganisms is gentamicin active against?

- Gram negative bacteria – e.coli, pseudomonas, proteus, klebsiella, serratia
- Gram positive – staph, strep (in combination with beta lactams)
- No anaerobic activity

What are the advantages of a single daily dosing regimen for gentamicin?

- Decreased toxicity time – less time above critical level for toxicity than multiple dose schedule
- Concentration dependent killing (at increased concentration can kill more bacteria at a faster rate)
- Post antibiotic effect (effects last longer than detectable serum levels)
- Easier to do outpatient therapy
- Cost effective
- Less nursing time
- What are the adverse effects of gentamicin?
- Nephrotoxic, ototoxic, prolongs neuromuscular blockade

How do penicillins enhance the efficacy of gentamicin?

- Transport of gentamicin into the cell is enhanced by penicillins because they act on the cell wall.

How does resistance to gentamicin develop?

- Transferase enzyme that inactivates drug
- Impaired cell entry via cell wall changes
- Alteration of ribosomal receptor proteins

6. Tetracyclines

Doxycycline

What is the MOA of doxycycline?

- Bacteriostatic
- Protein synthesis inhibitor - binds to the 30s subunit of a ribosome
- Blocks the binding of tRNA to mRNA ribosome complex and stops the addition of amino- acids to the peptide.
- Inhibits protein synthesis in malaria, where it is active against erythrocytic shizonts of all malaria parasites. Used for prophylaxis.

What are the pharmacokinetics of tetracyclines?

- A: generally well absorbed (>60% bioavailability) but absorption inhibited by food, calcium, dairy products and alkaline pH.
- D: Distributed widely to tissues except the CSF, crosses the placenta and can chelate to Ca in teeth and bones. 40-80% protein bound.
- M: Concentrated in bile, undergo enterohepatic circulation.
- E: Excreted in the bile and urine. Except for doxycycline which has no renal elimination.

What are the side effects of doxycycline?

- GI - nausea and vomiting
- Skin photosensitivity

- Hepatotoxicity
- Discolouration of teeth and bones (binds calcium in forming teeth ad bones so cannot be used in pregnancy or children <8yrs)
- Intracranial hypertension

Other than malaria, what are the other indications for doxycycline?

- Respiratory infections
- STIs (chlamydia, syphilis)
- Skin infections (acne)
- Rickettsia (Q Fever)
- Vibrio species (Cholera)
- Antihelminthis
- Anthrax
- Some gram negatives but not routinely used

7. Chloramphenicol

What is the mechanism of action of chloramphenicol?

- Chloramphenicol is bacteriostatic
- It directly interferes with substrate binding in the 50S subunit of the ribosome to block protein synthesis

What are the side effects of chloramphenicol?

- GIT: Nausea, vomiting, diarrhoea
- Bone marrow suppression
- Gray baby syndrome in newborns
- Drug interactions with phenytoin, warfarin

Which bacteria is it active against?

- Aerobic and anaerobic gram positive and negative. Rickettsia but not chlamydia.

8. Macrolides

Can you list some examples of macrolide antibiotics?

- Erythromycin, roxithromycin, azithromycin, clarithromycin

Describe the MOA of macrolides

- Bacteriostatic - at high concentrations can be bacteriocidal to some orgaisms
- Inhibit bacterial protein synthesis by binding to the 50s subunit of the ribosome, blocking transpeptidation.

What organisms are macrolides effective against?

- Gram positive organisms like staph, strep, pneumococcus

- Atypicals: mycoplasma, legionella, chlamydia, listeria and some mycobacteria
- Gram negative organisms: Neisseria, pertussis, treponema pallidum, campylobacter

What are the adverse effects of erythromycin?

- GI upset – anorexia, nausea, vomiting
- Liver toxicity – acute hepatitis
- Allergic reaction – fever, rash
- Drug interaction via P450 enzymes

What is the mechanism of the drug interactions with erythromycin and give some examples?

- Erythromycin inhibits hepatic enzymes, inhibiting the metabolism of other drugs and causing increased activity.
- Examples include benzodiazepines, digoxin, warfarin, theophylline

How does azithromycin differ from other macrolides?

- Higher tissue penetration
- Long elimination half life (2-4 days rather than 2-4 hours)
- Single daily dosing
- More effective against chlamydia, haemophilus
- Less effective against staph and strep
- Excreted unchanged in the urine
- No inhibition of of hepatic P450 so drug interactions are uncommon
- Prolongs the QT interval

9. Fluoroquinolones (cipro)

Ciprofloxacin

- Describe the pharmacokinetics of ciprofloxacin
- A: PO or IV administration, bioavailability >80%
- D: 20 - 40% protein bound
- E: Elimination half life 3-5 hours, renal elimination, requires dose adjustment in renal failure.

Describe the mechanism of action of fluoroquinolones

- Blocks DNA synthesis by inhibiting bacterial topoisomerase II (also known as DNA gyrase) and IV.
- Inhibition of Topoisomerase II - interferes with relaxation of supercoiled DNA, required for normal transcription and replication
- Inhibition of Topoisomerase IV - interferes with separation of replicated chromosomal DNA

What are the clinical uses of ciprofloxacin?

Used to treat UTIs, bacterial diarrhoea, soft tissue/bone/joint infections and atypical pneumonias or respiratory infections.

What is the microbial spectrum?

- Excellent gram negative activity, moderate gram positive activity
- Active against staph aureus, pseudomonas
- Agents of atypical pneumonia such as mycoplasma & chlamydia.
- Intracellular pathogens such as legionella & mycobacterium
- The drug of choice for treatment of anthrax

How does the antibacterial activity of ciprofloxacin differ from norfloxacin?

- Ciprofloxacin has a greater activity (4-8 times lower minimum inhibitory concentration) against gram negatives and has a much greater activity against gram positives

What are the potential adverse effects of fluoroquinolones

- Prolonged QT (with some)
- Nausea, vomiting, diarrhoea (including c.diff)
- Rash
- Abnormal LFTs
- Photosensitivity
- Hyperglycaemia in diabetes
- Damage to growing cartilage(not recommended for those <18 or in pregnancy/lactation)
- Tendonitis and risk of tendon rupture
- Allergy

What is the mechanism of resistance to fluoroquinolones?

Due to one or more point mutations in the quinolone binding region of the target enzyme or a change to the permeability of the organism.

10. Aciclovir

What are the indications for acyclovir in the ED?

- HSV encephalitis
- Varicella Zoster
- Patients with HIV
- Neonatal HSV

Describe the mechanism of action of acyclovir

- Inhibition of viral DNA synthesis via irreversible binding to DNA polymerase.
- Incorporation into viral DNA with termination.
- Specificity for virus-infected cell (virus specific thymidine kinase)

Describe the pharmacokinetics of acyclovir

- Short half life of 2.5hrs (5 times daily dosing PO)
- Low PO bioavailability
- Excreted unchanged in the urine
- CSF concentration reaches 50% of plasma concentration
- Large volume of distribution

Name some side effects of acyclovir

- Nausea, vomiting, diarrhoea
- Reversible renal toxicity
- Neurological effects - tremor, delirium, seizures

11. Tamiflu

List some anti-influenza agents

Oseltamivir, zanamivir, amantadine, rimantadine

What is the MOA of Osteltamivir/tamiflu?

- Neuraminidase inhibitor - disrupts viral replication and release.
- Active against influenza A and B

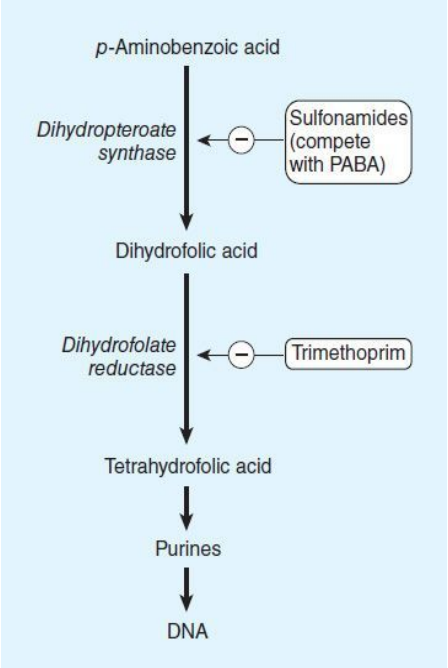
What is the relevance of these agents to emergency medicine?

- May be of use in higher risk groups i.e. pregnant women, immunocompromised
- Can limit the severity of disease in those infected
- Can be used in the early phases of a pandemic to limit spread and numbers infected

12. Trimethoprim/Sulphonamides

Describe the mechanism of action of trimethoprim.

- Selectively inhibits bacterial enzyme dihydrofolate reductase, which is required for the conversion of dihydrofolic acid to tetrafolic acid.
- By this mechanism it inhibits purine and DNA synthesis in the bacterium.
- Less efficient at inhibiting the human version of this enzyme.



What is the rationale for combining trimethoprim with sulphonamides?

- Sulphonamides inhibit sequential steps in the DNA synthesis pathway, leading to an enhanced effect.
- They inhibit the step before trimethoprim, which inhibits the conversion of PABA to dihydrofolic acid.

- This means the combination is bacteriocidal, compared to the bacteriostatic action of using just one.

13. Metronidazole

Describe the pharmacokinetics of metronidazole

- A: Well absorbed orally with 99% PO bioavailability, can also be given IV
- D: Low protein binding 10 - 20%
- M: Metabolised in the liver, can accumulate in liver disease
- E: half life 7.5 hours, excreted by the kidney

What are the adverse effects of metronidazole?

- GIT: nausea, diarrhoea, dry mouth, metallic taste
- Neuro: Headache, paraesthesia, dizziness
- Thrombophlebitis
- Disulfiram like effect so alcohol should be avoided

14. Chlorhexidine

What is an antiseptic?

A chemical disinfectant applied to living tissue which decreases the number of organisms by killing, removing or diluting and has generally low toxicity to tissues.

Describe the actions and uses of chlorhexidine

- Low skin irritating capacity
- Low oral toxicity
- Active against bacteria (most effective against gram positive cocci)
- Not inhibited by blood or organic products

When is chlorhexidine contraindicated

- Middle ear surgery (can cause sensorineural deafness)
- Neurosurgery as can cause neural toxicity
- Allergy