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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Drug causes teratogenesis Some common drugs and their potential teratogenic effect are given below: drug teratogenic effect Androgens cardiac deformities Alcohol fetal alcohol syndrome Carbamazepine microcephaly Diethylstilbestrol vaginal carcinoma Lithium cretinism Phenobarbital cleft palate Sodium valproate neural tube defects Thalidomide phocomelia Warfarin chondrodysplasia punctata

Unwanted drug effects in pregnancy

drug effects in pregnancy ACE inhibitors oligohydramnios, impaired renal function Aspirin kernicterus β-Blockers hypoglycaemia, intrauterine growth retardation, fetal bradycardia Carbimazole neonatal goitre NSAIDs close ductus arteriosus Sulphonamides kernicterus Thiazide diuretics: neonatal thrombocytopenia

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Antimicrobial

Antibiotics: bactericidal vs. bacteriostatic Bactericidal antibiotics Bacteriostatic antibiotics • penicillins • cephalosporins • aminoglycosides • nitrofurantoin • metronidazole • quinolones • rifampicin • isoniazid • chloramphenicol • macrolides • tetracyclines • sulphonamides • trimethoprim

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Antibiotics: mechanisms of action

The lists below summarise the site of action of the commonly used antibiotics
Inhibit cell wall formation Inhibit protein synthesis (by acting on ribosome) RNA synthesis peptidoglycan cross-linking 50S subunit

1. chloramphenicol
2. macrolides (e.g. • β-lactams
   Penicillins Cephalosporins • carbopenems

↓peptidoglycan synthesis erythromycin) 3. fusidic acid 4. (Quin/Dalfo)pristin 5. Linezolid 30S subunit • glycopeptides

1. aminoglycosides Vancomycin teicoplanin • Isoniazid

(Those organisms lacking a cell wall are resistant to these drugs eg. Chlamydia's) (cause misreading of mRNA) 2. tetracyclines

Antibiotics: anaerobic activity antibiotics have anti-anaerobic activity antibiotics do not have anti-anaerobic activity • penicillins • cephalosporins (except ceftazidime) • erythromycin • metronidazole • tetracycline

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Skin rash with antibiotics • Ampicillin and amoxicillin can cause skin rashes that are not allergic in nature • Erythromycin, benzylpenicillin, cefuroxime and cefadroxil all produce a diffuse, papular, non-purpuric rash that may be intensely pruritic • A maculopapular rash is also seen when tonsillitis/pharyngitis is related to EBV infection Cephalosporins • Cephalosporins are safe in penicillin allergy if it is only a rash. • Only ceftazidime and cefepime will cover Pseudomonas

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Co-trimoxazole Indications • now only indicated for oral prophylaxis against Pneumocystis pneumonia, toxoplasmosis and nocardiosis • It should only be considered in the treatment of chronic bronchitis or urinary tract infection where there is no other alternative

Side-effects • nausea, vomiting,
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Inhibit DNA synthesis Inhibit • quinolones (e.g. ciprofloxacin) Damages DNA
•Rifampicin

1. metronidazole Inhibits folic acid formation
2. sulphonamides
3. trimethoprim • gentamicin • ciprofloxacin • ceftazidime

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• allergy : rash (including Stephens-Johnson syndrome), toxic epidermal necrolysis and photosensitivity • Blood disorders: neutropenia, thrombocytopenia and, rarely, agranulocytosis Cautions/contraindications • used with caution (or avoided) in renal or hepatic impairment

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Aminoglycosides
Action • bactericidal antibiotics that bind to the 30S ribosome and inhibit bacterial protein synthesis. • active only against aerobic gram-negative bacilli and cocci. ineffective against anaerobic bacteria as they require O2 to enter bacterial cells. Indications • endocarditis in combination with penicillin (gentamycin) • added to a beta-lactam antibiotic when serious Pseudomonas aeruginosa (cystic fibrosis) • tuberculosis (streptomycin) Side effects • Nephrotoxicity
 The reversible acute tubular necrosis after aminoglycoside reflects a concurrent impairment in the concentrating ability, and most patients are non-oliguric. Irreversible tubulointerstitial damage, however, is uncommon after discontinuing aminoglycoside. We expect a diagnosis of acute renal failure beginning more than five days after the initiation of gentamicin;
 Aminoglycoside nephrotoxicity correlates with Frequency of aminoglycoside dosing
• Ototoxicity: Streptomycin, tobramycin, and gentamycin are primarily vestibulotoxic Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially cochleotoxic. Cochlear toxicity that results in hearing loss usually begins in the high frequencies and is secondary to irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea
 What is the explanation of progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment? Aminoglycosides are cleared more slowly from inner ear fluids than from serum monitor the patient for cochleotoxic and vestibulotoxic effects up to 6 months after cessation of aminoglycoside treatment is important. What is the initial manifestation of early hearing loss?
 increase in the threshold of highest frequencies (>4000 Hz).
 what is the main teratogenic effect of aminoglycosides. CN VIII toxicity

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• Transient myaesthenic syndrome Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis; large doses given during surgery have been responsible for a transient myaesthenic syndrome in patients with normal neuromuscular function. • What is the mechanism of resistance of Aminoglycosides? Bacterial transferase enzymes; they inactivate the drug by acetylation, phosphorylation or adenylation • Why is the gentamycin trough level likely to be too high in patients with chronic renal failure? Prolongation of the half-life The usual half-life of gentamicin is between 2 and 3 h, although this can be considerably prolonged in patients with renal failure. Administration • There are two commonly used regimens for dosing gentamicin. Both require the patient's body weight to ensure accurate dosing. For patients who are over their ideal body weight, this value rather than the patient's actual weight should be used. Ideal body weight can be calculated using age, sex and height on a number of online applications.

1. The most commonly used dosing regimen in the UK is the once daily regime, which is thought to be associated with reduced toxicity whilst being effective against gram-negative infections. It is not recommended for patients with a creatinine clearance of less than 60 ml/min. The dose used is 7 mg/kg IV every 24 hours. Levels should be monitored for patients on this regimen for 3 days or more, with a level taken 6-14 hours

following the third dose. A nomogram is then used to determine whether the interval between doses should be altered.

2. Patients with creatinine clearance of less than 60 ml/min are usually given a reduced dose of gentamicin with a multiple-daily dosing regimen. This may also be recommended by microbiologists for the treatment of serious gram-negative infections such as Pseudomonas. Dosing is dependent on creatinine clearance: >60 ml/min: 1.5-1.7 mg/kg IV every 8 hours 40-60 ml/min: 1.2-1.5 mg/kg IV every 12 hours 20-40 ml/min: 1.2-1.5 mg/kg IV every 12-24 hours <20 ml/min: 2 mg/kg loading dose then discuss with microbiology and pharmacy • On this regimen monitoring is typically initiated after the 3rd or 4th dose, which allows a steady-state to be reached. Peak levels should be taken 30 minutes following the end of the infusion, and a trough level taken before the next dose. The desired trough level is less than 2 micrograms/ml, with a peak level of 5-8 micrograms/ml. Administering gentamicin in conjunction with loop diuretics ↑↑ risk of exacerbating renal and ototoxicity

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• Aminoglycosides Ototoxicity: mechanism: cochlear dysfunction (e.g., tinnitus, hearing impairment) by damaging cochlear cells, and/or
 vestibulopathy (e.g., nausea, vomiting, dizziness, vertigo, oscillopsia, ataxia) by damaging hair cells of the inner ear. nystagmus may be present as an early sign. The vestibular dysfunction of gentamicin toxicity is typically bilateral; accordingly, there is no imbalance between right-sided and leftsided input to the central nervous system, so patients do not typically experience vertigo.
 However, patients can experience oscillopsia and an abnormal head thrust test in both horizontal directions. Oscillopsia is a visual disturbance in which stationary objects appear to oscillate. occur only when the head is moving.
Quick movements of the head are associated with transient visual blurring.
This can cause difficulties with seeing signs while driving or recognizing people's faces while walking.
 Head thrust test (Head impulse test) a physical examination maneuver to test for vestibular neuritis.
While the patient fixates on a target, the examiner administers brisk, horizontal head rotations to the side.
Considered positive if the patient is unable to maintain visual fixation, in which case the patient requires corrective saccades (quick eye movements) to re-fixate back to the target).

Macrolides • Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin. • They are used against intracellular pathogens, including Mycoplasma and Legionella, and can also be used as alternatives in case of penicillin allergy.
Action • Macrolides act by inhibiting bacterial protein synthesis by blocking translocation.
• Macrolides are bacteriostatic agents that inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome. If used in high doses, they may be bactericidal. • If pushed to give an

answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated. bacteriostatic at low doses and bactericidal at high doses

Macrolides (erythromycin, azithromycin and clarithromycin), aminoglycosides and chloramphenicol bind to bacterial ribosomes and disrupt protein synthesis

• Clarithromycin is a macrolide antibiotic with good gram positive cover and that of atypical

organisms. It's mechanism of action is via reversible inhibition of 50s ribosome subunit.

Mechanism of resistance • post-transcriptional methylation of the 23S bacterial ribosomal RNA Adverse effects • gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin • cholestatic jaundice: risk may be reduced if erythromycin stearate is used • P450 inhibitor (see below) Common interactions • statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis. • Clarithromycin enhances anticoagulant effect of coumarins This is because warfarin is metabolised by the same CYP3A isozyme as clarithromycin. Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. • Clarithromycin is a potent inhibitor of CYP3A4, and as such may interfere significantly with metabolism of a number of medications, including theophylline, simvastatin, and cyclosporine as the most important drug interactions. • The effect of warfarin and digoxin may also be potentiated by clarithromycin.

Erythromycin
• Was the 1st macrolide used clinically. Newer examples include clarithromycin and azithromycin.
• Erythromycin may potentially interact with amiodarone, warfarin and simvastatin • Erythromycin would inhibit the metabolism of theophylline. • Macrolides act by inhibiting bacterial protein synthesis.
• If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated. Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying Used in diabetic gastropathy,
Adverse effects of erythromycin • GI side-effects are common • Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used • P450 inhibitor
• associated with prolonged QT interval and torsades de pointes,

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Quinolones Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. Examples include: • ciprofloxacin • levofloxacin Mechanism of action

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• inhibit topoisomerase II (DNA gyrase) and topoisomerase IV Mechanism of resistance • mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration Adverse effects • lower seizure threshold in patients with epilepsy • tendon damage (including rupture) - the risk is increased in patients also taking steroids Rupture has been reported in the achilles, shoulder and hand. This may occur due to disruption of the extracellular matrix and depletion of collagen which is observed in animal models. • cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children Interaction & contraindication
• It should not be used with drugs that prolong the QT interval (eg erythromycin, tricyclic antidepressants) since there is an increased risk of cardiac arrhythmias • Contraindicated in left heart failure with reduced ejection fraction • It should not be given at the same time as bivalent or trivalent cations (eg aluminium, iron) as these reduce absorption. Antacids reduce quinolones absorption leading to therapeutic failure. • Quinolone absorption is markedly reduced with antacids containing aluminium, magnesium and/or calcium and therapeutic failure may result. Other metallic ion-containing drugs, such as sucralfate, iron salts, and zinc salts, can also reduce absorption. • The affinity of quinolones for the gamma-aminobutyric acid (GABA) receptor may induce CNS adverse effects; these effects are enhanced by some nonsteroidal anti-inflammatory drugs (NSAIDs).

Co-amoxiclav
• Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days. • If patient developed cholestatic jaundice the co-amoxiclav should be withdrawn, and the combination avoided in future.

Probenecid • Drugs can be excreted into the proximal convoluted tubule of the nephron by cation or anion transporters: cation transporters: basic drugs, eg quinine, pethidine, morphine anion transporters: acidic drugs, eg penicillins, bendroflumethiazide, furosemide, cephalosporins • The anion transporters are inhibited by probenecid, which can lead to increased plasma concentrations of acidic drugs • probenecid used clinically to increase the plasma half-life and therefore the therapeutic duration of the drug • For example, in the management of gonorrhoea infection, probenecid may be combined with oral penicillin to increase the half-life of the penicillin

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Sulfonamides Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis. Other uses • The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and

indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide. • Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease. • Co-trimoxazole: sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of

bacterial infections. The name cotrimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including Septra, Bactrim, and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic

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Vancomycin

Spectrum of the drug – MEC • M – MRSA • E – Enterococcus

• C - Cl. difficle Action • glycopeptide antibiotic • Bactericidal inhibits formation of peptidoglycan in bacterial cell walls, but a step earlier in the process compared to β-lactams binds D-ala-D-ala moities of the peptides
Resistance
• D-ala-D-ala mutates to D-ala-D-lac, conferring resistance Indications • IV administration for serious, multidrug resistant Gram-positive infections including methicillin-resistant Staphylococcus aureus infections (MRSA) including Enterococcus including multidrug resistant Staph epidermidis • Given orally for C. difficile not systemically absorbed when given orally when antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening;
• prophylaxis,
 for endocarditis following certain procedures in patients at high risk for endocarditis; for major surgical procedures involving the implantation of prosthetic materials or devices, e.g., cardiac and vascular procedures and total hip placement,
Side effects • Red man syndrome non-immunological reaction, related to the rate of infusion (infuse drug too fast → release of histamine → red rash) If a patient experiences an infusion related reaction to vancomycin:
 1.Cease infusion
 2. Administer antihistamine (cetirizine10mg PO)
 3. If newly hypotensive consider adrenaline
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Side effects – RON • R - Red man syndrome • O – Ototoxicity • N - Nephrotoxicity

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 4. recommencement of vancomycin at a slower rate of infusion (doubling the time to infuse the solution, or changing to a continuous infusion). • Ototoxicity more likely in patients with high plasma concentrations, renal impairment or pre-existing hearing loss. may progress after drug withdrawal, may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment. • Nephrotoxicity • Thrombophlebitis Dosage • loading dose: 25mg / kg (actual body weight) • Maintenance dose: 15 mg/kg per dose (actual body weight) (15mg/kg 12-hourly if GFR ≥40mL/min, (maximum 2 grams per dose) • When to start maintenance dose: According to GFR level: if GFR ≥ 40mL/min : 12 hours after loading dose if GFR = 20-

39 mL/min : 24 hours after loading dose If GFR < 20mL/min : check trough level 24 hours after loading dose; wait for trough result prior to re-dosing. Maintenance dose determination Monitoring • Vancomycin requires plasma level monitoring (after three or four doses if the renal function is normal, or earlier if renal impairment is present) • the best determinant of vancomycin efficacy is the AUC/MIC • A 24-hour AUC/MIC of 400 or more is the target for clinical success • AUC/MIC means: ratio of Area Under the Curve (plasma concentration vs time) to Minimum

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Inhibitory Concentration (Units are mg.hr/Litre) • For practical reasons, a trough (pre-dose) plasma concentration is used as a surrogate measure of efficacy.
• Trough level means: a serum vancomycin level taken at the end of the dosing interval, approximately one hour prior to next dose • The important level to measure here is the trough level as opposed to the peak level with gentamicin. • the target vancomycin trough level for the treatment of (MRSA) bacteremia is 15 to 20 µg/ml to achieve an AUC/MIC of 400 • The trough level toxic threshold (30 mg/l). If trough level > 30 mg/l Omit dose and restart when level <15 mg/l dose omission is required to reduce the risk of significant complications (including ototoxicity and nephrotoxicity).
 The BNF recommends trough levels of 15-20 mg/l for endocarditis. Intravenous administration • Doses of 1g should be administered over at least 60 minutes. For higher doses the duration of infusion should be extended by 30 minutes for each additional 500mg. This is recommended to reduce the risk of red man syndrome.
• The usual dilution is 5mg/mL; for fluid-restricted patients, concentrations of up to 10mg/mL may be used

Which molecular change is responsible for vancomycin resistance? D-ala D-ala to D-ala D-lac Vancomycin resistance is involves its Binding sites the D-Ala-D-Ala. terminal D-Ala is replaced by D-Lactate(D-Lac).

Linezolid
• is a type of oxazolidinones antibiotic class Action • inhibits bacterial protein synthesis by binding at the 50S subunit of the bacterial ribosome
 linezolid occupies the A site of the 50S ribosomal subunit, inducing a conformational change that prevents tRNA from entering the site and ultimately forcing tRNA to separate from the ribosome
 work on the first step of protein synthesis, initiation, unlike most other protein synthesis inhibitors, which inhibit elongation
• bacteriostatic Spectrum, highly active against Gram positive organisms including: • MRSA (Methicillin-resistant Staphylococcus aureus) • VRE (Vancomycin-resistant enterococcus) • GISA (Glycopeptide Intermediate Staphylococcus aureus)

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Advantages
• high bioavailability (close to 100%) when given by mouth:
 the entire dose reaches the bloodstream, as if it had been given intravenously.
Adverse effects • Bone marrow suppression (especially thrombocytopenia) (reversible on stopping) • Peripheral neuropathy • GI upset • Serotonin syndrome
Contraindications • Concurrent use with monoamine oxidase inhibitors (MAOI) and selective serotonin reuptake inhibitors (SSRIs)
• tyramine diet

Carbapenems
• Carbapenems are antibiotics used for multidrug-resistant (MDR) bacteria.
• members imipenem (+ cilastatin) normal kidneys break down imipenem with a dihydropeptidase cilastatin, a selective dihydropeptidase inhibitor, is always given with imipenem inhibits renal dihydropeptidase I, thereby decreasing inactivation of drug in renal tubules cilastatin not needed for meropenem meropenem • Their use is primarily in people who are hospitalized.
• Like the penicillins and cephalosporins, they are members of the beta lactam class of antibiotics, which kill bacteria by binding to penicillin-binding proteins and inhibiting cell wall synthesis.
• Side effect Gastrointestinal distress, skin rash and seizures are three common complications of carbapenem administration when there are high plasma levels. 5-10% of patients with penicillin allergy are also allergic to carbapenems Meropenem
• Which Carbapanem antibiotic has less CNS toxicity? Meropenem • Meropenem is a carbapanem antibiotic that does not need to be coadministered with Cilastatin.

Trimethoprim • Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections. • It is combined with sulfamethoxazole for synergistic reasons Mechanism of action • interferes with DNA synthesis by inhibiting dihydrofolate reductase Adverse effects • myelosuppression • transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug Trimethoprim interferes with tubular handling of creatinine and thereby leads to an increase in serum creatinine, without impairment of GFR. • Megaloblastic anaemia may occur owing to folate deficiency

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Quinupristin & dalfopristin antibiotics Overview • injectable streptogrammin antibiotic Only administered via a central line. • combination of group A and group B streptogrammin respectively. • inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome Spectrum • most Gram-positive bacteria • Particularly useful against multi- resistant Strep. pneumoniae and Staph. aureus. • exception: Enterococcus faecalis* Adverse effects • thrombophlebitis (give via a central line) • arthralgia • P450 inhibitor *not to be confused with Enterococcus faecium, which is sensitive to Quinupristin & dalfopristin

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Tuberculosis: drug side-effects and mechanism of action

Drug Most common side effects Rifampicin Orange bodily fluids, rash, hepatotoxicity, drug interactions Isoniazid Peripheral neuropathy, psychosis, hepatotoxicity Pyrazinamide Arthralgia, gout, hepatotoxicity, nausea Ethambutol Optic neuritis, rash

Rifampicin • mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA • potent liver enzyme inducer • hepatitis,
• orange secretions Patients on rifampicin should be warned that their urine, tears and other secretions will develop a bright orange-red colour • flu-like symptoms • acute interstitial nephritis (pt may present with acute renal failure after 1 month of starting rifampicin)

Interaction • Interact with oral contraceptive induces failure of the oral contraceptive treatment • Rifampicin is a potent hepatic enzyme inducer that increases the metabolism of many drugs, including all the steroid hormones • Barrier contraceptives must be used during treatment with rifampicin and for 4-8 weeks after a course of rifampicin is completed

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Isoniazid

• mechanism of action: inhibits mycolic acid synthesis • peripheral neuropathy:
 Occurs in less than 1% Those with N-acetyltransferase type-2 gene defect resulting in abnormal isoniazid metabolism predisposed to neuropathy Prevented with 10 mg pyridoxine (Vitamin B6) • hepatitis, raised transaminases in 10-20% Isoniazid-induced hepatitis occurs in ~1% of individuals and is much commoner in people more than 35-years-old (risk of hepatitis is less than 0.3% in patients under 20 years; 2-3% risk in individuals over 50 years). • agranulocytosis • liver enzyme inhibitor • isoniazid inhibits the conversion of tryptophan to niacin nicotinic acid (niacin) deficiency Pellagra (the 3 D's - dermatitis, diarrhoea and dementia) • systemic lupus erythematosus (SLE)-like syndrome. • Isoniazid toxicity
 Isoniazid toxicity should be suspected in any patient with intractable seizures and profound metabolic acidosis with an elevated anion gap. Intravenous pyridoxine (vitamin B6) is the treatment of choice. The acidosis may need to be corrected with bicarbonate.

Pyrazinamide • mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I • hyperuricaemia causing gout • arthralgia, myalgia • hepatitis Ethambutol • mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan • optic neuritis: check visual acuity before and during treatment • dose needs adjusting in patients with renal impairment The main adverse effects of ethambutol are: loss of visual acuity restriction of visual fields colour blindness retrobulbar neuritis
 arthralgia.

Uncommonly it may be associated with hyperuricaemia, and with interstitial nephritis. This is thought to occur less frequently than with rifampicin.

Antiviral agents Drug Mechanism of action Aciclovir Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase Ganciclovir Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase Ribavirin Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA Amantadin e Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings Oseltamivir Inhibits neuraminidase Influenza Foscarnet Pyrophosphate analog which inhibits viiral DNA polymerase Interferon-α Human glycoproteins which inhibit synthesis of mRNA Cidofovir Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir) Which step is required for acyclovir activation? Conversion to monophosphate form by viral thymidine kinase Notes & Notes for MRCP
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Adverse effects/toxicit y Indication s HSV, VZV Crystalline nephropathy CMV Myelosuppressio n/agranulocytosis Chronic hepatitis C, RSV Haemolytic anaemia Influenza, Parkinson's disease Confusion, ataxia, slurred speech CMV, HSV if not responding to aciclovir Nephrotoxicity, hypocalcaemia, hypomagnasaem ia, seizures Chronic hepatitis B & C, hairy cell leukaemia Flu-like symptoms, anorexia, myelosuppressio n CMV retinitis in HIV Nephrotoxicity

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HIV: anti-retrovirals Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging Anti-retroviral agent used in HIV About Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI) Examples: zalcitabine, zidovudine (AZT), didanosine,

lamivudine, stavudine, Protease inhibitors (PI) • Inhibits a protease needed to make virus able to survive outside the cell • Examples: indinavir, nelfinavir, ritonavir, saquinavir Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) examples: nevirapine, efavirenz

Nucleoside analogue reverse transcriptase inhibitors (NRTI) • examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine • general NRTI side-effects: peripheral neuropathy • zidovudine: anaemia, myopathy, black nails • didanosine: pancreatitis Non-nucleoside reverse transcriptase inhibitors (NNRTI) • examples: nevirapine, efavirenz • side-effects: P450 enzyme interaction (nevirapine induces), rashes Protease inhibitors (PI) • Protease inhibitors are multi-pathway inhibitors of rivaroxaban clearance and elimination. • examples: indinavir, nelfinavir, ritonavir, saquinavir • side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450

enzyme inhibition • indinavir: renal stones, asymptomatic hyperbilirubinaemia • ritonavir: a potent inhibitor of the P450 system

HIV: anti-retrovirals - P450 interaction • nevirapine (NNRTI): induces P450 • protease inhibitors: inhibits P450 Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors. Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

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Oseltamivir (Tamiflu) • Oseltamivir (Tamiflu) like its predecessor zanamivir (Relenza) functions as an antiviral through inhibition of the enzyme neuraminidase, thus slowing viral replication down rather than directly killing the virus particle. • This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus. • Unlike inhaled zanamivir, oseltamivir is administered orally. • Oseltamivir It is of value in prophylaxis against influenza • However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and preferably within 48 hours.

Anti-fungal • Nystatin is poorly absorbed through mucous membranes and is thus useful in oral, vaginal and enteric candidiasis • Terbinafine is used to treat superficial mycoses such as dermatophyte infections • Fluconazole is useful in candidiasis and central nervous system infections with Cryptococcus neoformans and is usually commenced after initial treatment with amphotericin and flucytosine • Itraconazole is the agent of choice for non-life threatening blastomycosis and histoplasmosis it is also moderately effective against invasive aspergillosis • Amphotericin B treatment of Aspergilloma The drug may exert either fungicidal or fungistatic activity, depending on its concentration at the site of infection and sensitivity of the organism increases the permeability of the fungal cell wall by binding to ergosterol and forming micropores side effect nephrotoxicity associated with hypokalaemia and hypomagnesaemia To decrease toxicity, newer lipid-bound preparations are now available

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Griseofulvin
• Is not active against Candida albicans. It is active against trichophytons (tinea) and other dermatophytes. • It is metabolised in the liver (note also it's an enzyme inducer). Only 0.1-0.2% excreted in urine. • Treatment with griseofulvin is often needed for a long period, sometimes years, depending on the rate of nail growth. • It is associated with drug-induced Stevens-Johnson syndrome

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Diethylcarbamazine Indication: • Treatment of individual patients with certain filarial diseases. • These diseases include: lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; (ELEPHANTiasis) tropical pulmonary eosinophilia, and loiasis.

Pharmacology

Overdose of antimalarial medications Chloroquine Symptoms • Nausea • Headaches • Visual disturbances • Cardiac arrhythmias • Convulsions • Coma

Treatment • Activated charcoal should be given to patients who present within 1 h • The initial hypokalemia that occurs appears to be cardio-protective and should not be corrected for at least 8 h after the ingestion • In patients with severe toxicity, high-dose (2 mg/kg) diazepam and adrenaline (0.25 pg/kg per min) have been shown to reduce mortality

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Quinine toxicity (cinchonism)

• Indications of Quinine: antimalarial prophylactic agent against leg cramps,
• The effect of Quinine toxicity, (known as cinchonism), may be fatal: In the short term: cardiac arrhythmia (common) (ventricular tachyarrhythmias or fibrillation) due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively flash pulmonary oedema Hypoglycaemia (common)
 quinine stimulates pancreatic insulin secretion Visual complications, including blindness, can occur and may be permanent in the long term renal failure
• Differential diagnosis (Quinin vs Aspirin) Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen.
 Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.
 In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods. • Management
 Supportive fluids, inotropes and bicarbonate as needed
 positive pressure ventilation for pulmonary oedema. Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed, dry skin and abdominal pain.

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 Avoid Lidocaine (lignocaine) should not be used in the management of cardiac arrhythmias as this can increase the risk of seizures Urine acidification is not recommended as whilst it increases quinine elimination, it also increases the risk of cardiotoxicity

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Immunosuppressants

Ciclosporin (Cyclosporine)

Mode of action • It acts by binding to cyclophilin forming a complex which inhibits calcineurin, (a phosphotase that activates various transcription factors in T cells) reducing IL-2 release decreases clonal proliferation of T cells immunosuppression

Indications • following organ transplantation • rheumatoid arthritis • psoriasis (has a direct effect on keratinocytes as well as modulating T cell function) • ulcerative colitis • pure red cell aplasia • atopic dermatitis (AD) (T lymphocytes are involved in the pathophysiology of AD and increased production of cytokines particularly IL-4)

Adverse effects (note how everything is increased - fluid, BP, K+, hair, gums, glucose) • Nephrotoxicity Chronic interstitial nephritis is a major side-effect of ciclosporin Fluconazole inhibits the metabolism of ciclosporin which increases the risk of ciclosporin nephrotoxicity. • hepatotoxicity • fluid retention • hypertension • hyperkalaemia • hypertrichosis • gingival hyperplasia • impaired glucose tolerance • hyperlipidaemia • increased susceptibility to severe infection

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• Tremor cause coarse tremor.
 In the first instance the dose should be reduced.
 Usually the neurological side effects of cyclosporin are dose dependent. • increased risk for Squamous cell carcinoma
 Cutaneous squamous cell carcinoma (SCC) is the second most common human cancer transplant-associated SCC (TSCC), which occurs in immune-suppressed solid organ transplant recipients (OTRs) may be considerably more aggressive than SCC in immune competent patients, with metastatic rates as high as 8% IL-22 receptor is most highly expressed in TSCC and is induced by cyclosporine A. Treatment with anti–IL-22 antibody decreases SCC tumor number and tumor burden. Note: • Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

Cyclosporine A immunosuppression drives catastrophic squamous cell carcinoma through IL-22 (September 2016)

Monitoring • These patients are seen monthly to have their blood pressure, urea, and electrolytes checked. • indications for stopping cyclosporine treatment:
 Difficult to control hypertension
 increase in creatinine by more than 30% from baseline

Tacrolimus Mode of action • similar to the action of ciclosporin
Tacrolimus vs Ciclosporin:
• It has a very similar action to ciclosporin (inhibits calcineurin, reducing IL-2 release) • The action

of tacrolimus differs from ciclosporin in that it binds to a protein called FKBP rather than cyclophilin
• Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less.
• However, nephrotoxicity and impaired glucose tolerance is more common Indications • immunosuppressant to prevent transplant rejection. • Other T-cell medicated diseases Eczema (as ointment)
 Sever refractory uveitis after bone marrow transplant Vitiligo
Monitoring • Tacrolimus levels can be affected by concomitant use of other drugs and changes in gut absorption, and so need to be monitored carefully. Many side effects of tacrolimus are similar to cyclosporine A, but tacrolimus does not cause gingival hyperplasia or hirsutism

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Sirolimus
Overview
• A macrolide compound
• Also known as rapamycin Mode of action • binding with intracellular FKBP-12 protein inhibition of mTORC1 ↓ cytokine-induced T-cell proliferation immunosuppression
• Sirolimus binds to the immunophilin FK binding protein 12 (FKBP12), and the drugimmunophilin complex acts on the Target of Rapamycin (rapamycin being the original name of sirolimus) to interrupt stimulation of cell proliferation via the interleukin-2 receptor. • What is the target of action of sirolimus? FK binding protein 12 (FKBP12) Indications • treatment of acute rejection.
Adverse Effects • Pancytopenia • Hyperlipidemia
• Peripheral edema • Insulin resistance Inhibition of mTORC2 diabetes- like symptoms

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Azathioprine

Azathioprine check thiopurine methyltransferase deficiency (TPMT) before treatment • Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis Impaired DNA synthesis • A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity. The enzyme activity of thiopurine methyltransferase (TPMT) is under the control of a genetic polymorphism. 90 % of the population have normal or high (TPMT) enzyme activity. 10 % have intermediate levels One in 300 people have no functional enzyme activity. Several groups of patients have developed azathioprine induced myelosuppression linked to TPMT deficiency.

Adverse effects include • bone marrow depression Pancytopenia
 It suppresses lymphocyte numbers and function • nausea/vomiting • pancreatitis • Hepatotoxicity • 100-fold increased risk of skin cancers and lymphomas.

Monitoring • (BNF) suggest monitoring CBC, LFTs and U&E every 3 months once patients are established and stable on azathioprine treatment.

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interaction • Azathioprine and 6-MP are metabolized by xanthine oxidase. Therefore, allopurinol–a xanthine oxidase inhibitor–increases the risk of azathioprine and 6-MP toxicity. • A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used. Allopurinol acts by inhibition of xanthine oxidase and thus inhibits the metabolism of 6-mercaptopurine, an active metabolite of azathioprine. The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.
 Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.
 Co-administration of (Azathioprine + Allopurinol) accumulation of 6-MP (6-MP toxicity) ↑ risk of myelosuppression (aplastic anaemia) if concomitant use is to occur, a dose reduction in azathioprine by 25% is advised with regular blood count monitoring.
Usage in pregnancy • Azathioprine can be used in pregnancy without significant risk to the fetus

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Methotrexate Action • Methotrexate is an antimetabolite which inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines Methotrexate inhibits dihydrofolate reductase , thereby inhibiting the production of tetrhydrofolate required for thymidine and purine synthesis.
 inhibits purine and pyrimidine synthesis by competing for the active site of dihydrofolate reductase (by competitive inhibition). It is cytotoxic during the S-phase of the cell cycle, and has a greater toxic effect on rapidly dividing cells. Take 6 -12 weeks to achieve full affect
Indications • rheumatoid arthritis • psoriasis (Methotrexate would be the only correct treatment for someone with erythrodermic psoriasis) • acute lymphoblastic leukaemia Adverse effects • mucositis • myelosuppression • Macrocytosis is seen as a consequence of long term methotrexate therapy. • pneumonitis • pulmonary fibrosis • liver cirrhosis What is the toxicity of Methotrexate (MTX) at the liver? Macrovesicular fatty change Pregnancy • women should avoid pregnancy for at least 3 months after treatment has stopped • the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment Prescribing methotrexate • methotrexate is taken weekly, rather than daily

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• FBC, U&E and LFTs need to be regularly monitored.
 The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months' • Folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose • the starting dose of methotrexate is 7.5 mg once weekly, can be increased by 2.5 mg every 6 weeks, to a maximum of 20 mg weekly (Ref: oxford handbook of practical drug therapy) • only one strength of methotrexate tablet should be prescribed (usually 2.5 mg) • do not prescribe with aspirin or NSAIDs ↓ methotrexate excretion ↑ toxicity
• avoid prescribing anti-folate antibiotics trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia • In the circumstances of infection one should consider temporarily stopping

methotrexate as it is an immunosuppressant. Interaction • OAT-1 inhibitors
 Methotrexate is a substrate for the OAT-1 renal transporter and levels of methotrexate are therefore affected by decreased renal function.
 OAT-1 inhibitors include drugs such as probenecid, and therefore should not be used in conjunction with methotrexate.
• Omeprazole
 Omeprazole is also known to affect clearance of methotrexate; this interaction is not thought to be via OAT-1, but is thought to be related to inhibition of breast cancer resistance protein, which is responsible for methotrexate transport. Monitoring
• Clinicians are recommended to check FBC fortnightly until 6 weeks after the last dose increase.
 Provided it is stable, it can be checked monthly thereafter until the dose and disease is stable for one year. Thereafter, monitoring is guided by clinical judgement. If white cell count is less than 3.5, neutrophils less than 2 or platelets less than 150, methotrexate should be withheld pending discussion with the specialist team. An MCV greater than 105 fL warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team. • Liver function tests should be checked three monthly. If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed. • Urea, creatinine and electrolytes should be checked six monthly. If the estimated glomerular filtration rate falls below 50 mL/minute, methotrexate should be withheld until the result has been discussed with the specialist team. Drug MOA Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase Azathioprine metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. purine synthesis inhibitor Methotrexate antimetabolite which inhibits dihydrofolate reductase

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Methotrexate overdose Methotrexate overdose Folinic acid

• Methotrexate is a folic acid antagonist which can result in multi-organ failure in overdose. • medication errors with respect to rheumatoid arthritis are not uncommon.
 Patients occasionally find it difficult to understand that they must take their medication weekly as opposed to daily.
• Calcium folinate is a potent antagonist for the effects of methotrexate on the haematopoeic system, given by IV infusion at doses up to 75mg in the first 12hrs. This can then be followed by doses of 6-12mg every 4hrs.
• Folinic acid is the antidote and should be given intravenously as soon as possible, regardless of the liver function tests. • Blood transfusion may also be required in exceptional circumstances.
• Where massive overdose of methotrexate has occurred, hydration and urinary alkalinisation may be an option.
• Standard dialysis is ineffective in removing methotrexate, although intermittent high flux dialysis may be of value.

Mycophenolate mofetil Mode of action • inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells • A growing number of studies have demonstrated the efficacy of mycophenolate in SLE, especially in the context of lupus nephritis.
• Mycophenolate is an anti-purine drug that selectively depletes B and T lymphocytes (preferentially targeting activated cells). The result of this mode of action is that neutropenia is rare, which would be advantageous in (SLE) patients complicated by an autoimmune neutropenia.
 the most appropriate agent for (SLE) which complicated by an autoimmune neutropenia • adverse effects
 Pancytopenia Hypertension Hyperglycemia

Hydroxychloroquine
• Hydroxychloroquine ocular toxicity includes:
 Keratopathy
 Ciliary body involvement
 Lens opacities (Lenticular deposits)
 Retinopathy.
 Retinopathy is the major concern; the others are more common but benign.
 The incidence of true hydroxychloroquine retinopathy is exceedingly low.
 Risk factors include:
 Daily dosage of hydroxychloroquine
 Cumulative dosage
 Duration of treatment Coexisting renal or liver disease

 Patient age, and Concomitant retinal disease.
 Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia.
 They can also be asymptomatic.
 Most patients with advanced retinopathy have a bull's eye (also known as target, as in darts) fundoscopic appearance. All patients have field defects including paracentral, peri-central, and central and peripheral field loss.
• Regular screening may be necessary to detect reversible premaculopathy.
• Cessation of the drug is the only effective management of the toxicity.

Sulfasalazine
Side effects
• hypersensitivity,
• myelosuppression,
• macrocytosis, and
• azoospermia in males.
sulfasalazine toxicity • There are numerous signs of sulfasalazine toxicity.
• Rash and oral ulceration should be asked about and, if severe, the drug should be withheld until

specialist advice has been sought.
• Nausea, dizziness and headache can be common and sometimes necessitate dose reduction.
• If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.
Monitoring
• CBC
 CBC should be monitored monthly for the first 3 months.
 Sulphasalazine should be withheld until discussion with the specialist team if:
 The white cell count is less than 3.5
 Neutrophils is less than 2, or
 Platelets are less than 150.
 If (MCV) > 105 fl, vitamin B12, folate and TSH should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.
 If counts remain normal within the first 3 months, CBC can be checked 3 monthly.
• Liver function tests (LFTs)
 should also be checked monthly for the first 3 months. If either AST or ALT are more than twice the upper limit of normal, sulfasalazine should be withheld until discussion with the specialist team.
 If the LFTs remain normal for the first 3 months, monitoring can be decreased to 3 monthly.