

LIVER DISEASE

Affects over 2million people in UK

Main cause: alcohol, obesity, undiagnosed hepatitis infection from viruses, drug or chemical toxicity

Alcohol related liver disease	Cause fatty liver
Drug toxicity	Paracetamol poisoning – overdose or other recreational drugs
Hepatitis (inflammation)	Inflammation of hepatocytes (from alcohol, overdose, recreational drugs)
Non-alcoholic fatty liver disease (NAFLD)	Due to obesity
Cirrhosis	Late-stage liver diseases hepatocytes are dying
Cancer	Late stage of liver disease
Gallstones	Stop Biles form being secreted e.g., gallstones in bile duct -> can be removed
Cholangitis	Inflammation of bile duct itself – narrowing of the bile duct causing bile not secreted
Hemochromatosis	Iron overload, inherited – iron being laid down in the tissues
Wilson's disease	Copper overload, inherited – copper ends up damaging the liver
Gilbert's disease	Inability to metabolise bilirubin properly - Waste product of heme (breakdown of RBC)

What can cause liver disease?

Cause 1: Viruses	Cause 2: Drugs	Cause 3: Alcohol
<ul style="list-style-type: none"> Hepatitis A (self-limiting) – faecal oral route, vaccine available Hepatitis B – body fluids, drug abuse, mother to baby, acute -> chronic, cirrhosis and cancer, vaccine – given to staff in hospital settings Hepatitis C – body fluids, chronic and may progress to cirrhosis and cancer, no vaccine Hepatitis D – body fluids, requires concomitant infection with hep B to survive Hepatitis E (self-limiting) – contaminated food & water Hepatitis G – body fluids, chronic infection similar to HCV 	<ul style="list-style-type: none"> Paracetamol overdose Even when appropriately prescribed: <ul style="list-style-type: none"> Statin Antibiotics e.g., amoxicillin, tetracycline Methotrexate – immunosuppressant Natural <ul style="list-style-type: none"> Herbal remedies e.g., kava kava Vitamin A high dose Wild mushrooms 	<ul style="list-style-type: none"> Directly toxic to liver cells Causes inflammation -> fatty liver -> fibrosis Fibrosis alters structure and blood flow -> portal hypertension and liver failure Damage occurs >40g/d in men (2pints) and >20g/d in women (1pint) <14 units per week (half a pint per day) one pint = 2 units Spread over at least 3 days do not binge drink

ACUTE LD: caused by drugs or virus usually self-limiting – results in hepatocytes inflammation/damage – occasionally severe resulting in liver failure

Symptoms: possibly asymptomatic, generalise malaise (discomfort), anorexia, fever, jaundice (later)

CHRONIC LD: commonly caused by alcohol abuse – inflammation present for longer than 6 months – results in permanent damage with structural changes – cirrhosis (loss of function of hepatocytes)

Symptom: fatigue, weakness, loss of weight, nausea/vomiting, loss of appetite, cachexia (waste of muscle in arms and legs), abdominal swelling, right upper quadrant abdominal pain and tenderness, jaundice, bleeding from gums/nose and easy bruising (not producing clotting factors)

- ➔ Specific depending on type of disease e.g., gallstones – upper abdominal pain + vomiting after eating a greasy meal + if infected fever
- ➔ With cirrhosis (later stage disease) develop progressive symptoms as liver fails
 - Inability to metabolise waste – lead to toxins as bilirubin build causing jaundice
 - Failure to produce proteins required for body function
 - Lack of clotting factors 2,7,10 =bleeding,
 - No production of albumin = swelling

- Symptoms of easy bruising, gynecomastia (increase in male breast size), impotence, confusion, ascites (abdominal swelling), portal hypertension (build-up of blood pressure in the portal tract), oesophageal varices (bleeding)

LIVER DAMAGE STAGES				
Normal Liver	Fatty Liver	NASH Liver	Cirrhotic Liver	Hepatocellular Carcinoma
	<ul style="list-style-type: none"> Increased triglycerides Increased LFTs Increased liver fat Hepatic cells starts to die 	<ul style="list-style-type: none"> Early stage of liver disease Steatosis Ballooning Inflammation Fibrosis 	<ul style="list-style-type: none"> Cirrhosis Note reversible to a normal liver Late stage of fibrosis 	Liver cancer
	Reversible condition	Can be resolved if remove the underlying cause or take antifibrotic drug	Eligible for liver transplantation	

1. Lots of hepatic stellate cell causing lots of extracellular matrix and fibrosis
 2. Infiltrating lymphocytes
 3. Activated Kupffer cells trying to phagocytose dead cells
 4. Dying hepatocytes
 5. Sinusoid lumen has an increased resistance to blood flow bc of fibrosis and scarring

What is cholestasis?

Liver cells not producing and secreting bile and lack of bile getting into the GI track

- ➔ Due to hepatocytes: failure of bile production and secretion – causes include hepatitis from viruses, alcohol, drugs, pregnancy
- ➔ Due to bile duct: failure of outflow via bile duct due to obstruction such as gallstones, carcinoma, cholangitis (scarring and progressive inflammation – narrowing, so bile cannot get out)

Signs and complications of Liver Disease	
Jaundice	Yellow discolouration of skin & mucous membranes (sclera) Cause: <ul style="list-style-type: none"> - Haemolysis (haemolytic jaundice) – break down of RBD not getting rid of heme hence build-up of bilirubin in skin - Hepatocellular damage (hepatocellular jaundice) - Cholestasis (obstructive jaundice) – bile is being made in liver, but can't get rid of it due to obstruction in bile duct
Portal Hypertension & Oesophageal varices	Due to fibrosis, there is resistance of blood flow causing back flow High blood pressure pushes blood into surrounding blood vessels – thin-walled veins in oesophagus - oesophageal varices (swollen veins) If pressure too high – can rupture, bleed leading to hypovolemic shock and death
Ascites	Accumulation of fluid in peritoneal cavity due to pressure imbalance between high circulation on the inside and low pressure in peritoneal cavity ➔ Fluid will move from high pressure to low causing build-up of fluid in peritoneal cavity Cause: <ul style="list-style-type: none"> - Portal hypertension - Low plasma albumin (as one of its roles is to increase osmolarity pressure) - Salt and water retention by the damaged kidney e.g., secondary hyperaldosteronism

Hepatic encephalopathy	<ul style="list-style-type: none"> → Build-up of ammonia in the blood stream causing neurological damages as it passes BBB → Breakdown of amino acid in the gut via colonic flora (gut bacteria) create ammonia and it is made to urea in the liver for excretion – if excess due to liver problems → Symptoms: Altered mental state, fetor hepaticus (breath that has a strong musty smell), asterixis (hand tremor), drowsiness, confusion, coma → Due to ammonia & nitrogenous substances from gut by passing liver & crossing BBB → Increased risk with dehydration, hypovolaemia, GI bleed, CNS drugs, alcohol, increased dietary protein and constipation
Wernicke encephalopathy	<ul style="list-style-type: none"> → Due to deficiency of thiamine, with decreased mental function → Occurs in chronic alcohol abuse
Haematological changes	<ol style="list-style-type: none"> 1) Anaemia - Effect on iron homeostasis <ul style="list-style-type: none"> - Splenomegaly from portal hypertension – megaloblastic anaemia (a blood disorder when bone marrow produces stem cells that make abnormally large RBC) - Alcohol toxic to bone marrow 2) Bleeding and bruising <ul style="list-style-type: none"> - Reduction in clotting factor synthesis (2,7,10)
Circulatory and skin changes → More than three of these problems are a sign of liver disease	<p>Circulatory problems:</p> <ul style="list-style-type: none"> - Palmar erythema: looks like dermatitis w/o dryness just redness - Spider naevi: due to back pressure into smaller blood vessels - Finger clubbing: due to changes in interstitial fluid (also in lung cancer) <p>Skin</p> <ul style="list-style-type: none"> - Pruritis: itching skin due to toxic substances not being broken down in the liver and travelling to skin e.g., bilirubin

DIAGNOSIS OF LIVER DISEASE

Medical history taking of signs and symptoms

Blood test: LFTs, electrolytes, full blood count (end stage – bone marrow suppression will have low RBC, WBC and platelets), viral screens, blood clotting (PT prothrombin time)

Imaging: ultrasound, CT scan, MRI – enables clinician to assess the functionality of its structure of the organs relating to the liver e.g., gall bladder, bile ducts, liver cancer or fatty liver?

Liver Biopsy: local anaesthetic + long needle through chest into liver + sample from liver taken for microscopy

Liver Function Tests (LFTs)		
	Reference Range	Note
Aspartate Transaminase (AST)	5-40 IU/L	Role in gluconeogenesis – catalyses reversible conversion of aspartate and alpha keto glutarate -> oxaloacetate and glutamate Found in hepatocytes but also in other tissues (heart, brain, skeletal muscle) – thus never blood test alone, always take other history
Alanine transaminase (ALT)	5-30 IU/L **this is more specific to liver	Role in gluconeogenesis - catalyses reversible transfer of an amino group from L-alanine -> alpha ketoglutarate -> pyruvate and L-glutamate <ul style="list-style-type: none"> - Very high level in acute viral/toxic hepatitis - High levels in cholestatic jaundice/cirrhosis – degree of rise is some indication of degree/extent of liver damage - AST/ALT ratio is useful in diagnosis different types of liver disease: AST/ALT>2 alcohol injury, other liver injuries AST/ALT <1

Gamma glutamyl transferase (GGT)	5-45 IU/L	Catalyses transfer gamma glutamyl moiety of glutathione -> amino acid, peptide or water (forming glutamate) Very high levels in biliary obstruction, lower increased levels in chronic alcohol or drug toxicity, hepatitis, cirrhosis, or cholestasis <ul style="list-style-type: none"> - Indicator of alcohol abuse – GGT level will be elevated with alcohol but drop with 3-6 weeks of abstinence <p>Also in kidney, pancreas prostate</p>
Alkaline phosphatase (ALP)	20-100 IU/L	Removes phosphate groups from nucleotides, proteins and alkaloids Very high levels in biliary obstruction Also in bone, intestinal wall, renal tubules, placenta (will also be elevated for disorders of these organs)
Bilirubin	0-17 umol/L Jaundice occurs in >35 umol/L	Reflects depth of jaundice, thus useful for monitoring disease progression Can measure conjugated/unconjugated or request total bilirubin levels <ul style="list-style-type: none"> - Will differentiate the type of disease - When RBC broken down, release haemoglobin then is converted to unconjugated bilirubin (bound to albumin in the blood and travels to the liver – then conjugated w/ glucuronic acid (glucoronate) for excretion in bile) - Increased unconjugated if excessive RBC breakdown - Increased conjugated if issue with liver itself
Plasma proteins and albumin	60-80g/dL total protein 35-50g/fL albumin	Albumin is synthesised solely by the liver <ul style="list-style-type: none"> - Half-life of plasma albumin is 20-26 days tf, reduction in level indicate long term damage to the liver - <20g/dl results in oedema – changes in plasma protein pressure
Prothrombin time (PT)	10-15 sec	A measurement of how long it takes to blood clot When clotting factors (2,7,10) are reduced PT increase <ul style="list-style-type: none"> - These factors need vit K for their production, vit K is fat soluble, which needs bile salts for absorption tf, administration of vit K can differentiate where the underlying problem is <p>After administration of vit K</p> <ol style="list-style-type: none"> 1) Hepatocellular damage: PT unresponsive to vit K - Bc, liver still unable to produce clotting factors 2) Cholestasis (have increased PT): will be responsive to vit K and have decrease PT (improvements) - Now know its due to lack of vit K absorption due to deficiency of bile salts hence with vit K administration increased clotting factor production improving PT
Urea and ammonia	2.5-7.8 mmol/L Urea 16-60 (M), 11-51 (F) umol/L ammonia	Urea decreased in liver disease – bc reduction in synthesis by liver Ammonia increased in liver disease – hepatic encephalopathy (failure of liver to convert ammonia to urea for excretion hence causing cognitive issues)

DRUG HANDLING with LIVER IMPAIRMENT

Affect: drug clearance, biotransformation, pharmacokinetics

Most of the time this can increase the bioavailability of the drug and tf normal doses can potentially have toxic effects in patient with liver disease -> but the levels vary depending on individual drugs, patients, injury and severity (unlike renal disease where there is specific dose modification according to function)

- Inhibition and induction of drug metabolising enzymes (CYP450) are the most frequent and dangerous drug-drug interaction
- Thus, close monitoring the effects of drug and plasma concentration crucial (therapeutic & toxic)

Factors responsible include alterations in:

Intestinal absorption	
Reduced plasma protein binding	Due to the reduction in synthesis of plasma – increases the levels of normally high protein bound medication
Reduced hepatic extraction ratio	
Reduced liver blood flow	
Formation of portal systemic shunting	As a consequence of formation of the collateral circulation (due to portal hypertension) – collateral circulation bypasses the liver and can increase the bioavailability of certain drugs
Biliary excretion	
Enterohepatic circulation	
Renal clearance	As a consequence of the disturbance of liver anatomy due to liver disease – reduction in renal blood flow – affect renal formation

Actual rate of drug removal by liver is dependent on metabolism capacity and extraction ratio

- 1> Metabolism – make it more polar, less lipid soluble to aid excretion from body

Phase I	Phase II – addition of large polar groups to aid excretion
Oxidation - azathioprine	Glucuronidation – paracetamol, morphine
Reduction - halothane	Sulphonation – steroids
Hydrolysis - atropine, pethidine	Acetylation – hydralazine, phenelzine Methylation - nicotine
2> Excretion Ratio – actual rate of drug removal by the liver	
HIGH close to 1	LOW close to 0
- Clearance depends on hepatic blood flow - First pass metabolism - Likely to require greater reduction in dose, but no guidance E.g., chlormethiazole, lignocaine, morphine, propranolol, verapamil, metoprolol, pethidine	- Clearance depends on metabolising capacity of liver E.g., chlorpropamide, phenytoin, diazepam, warfarin, atenolol, frusemide, prednisolone, lorazepam

Pharmacokinetic issues		Pharmacodynamic issues
Cytochrome P450		
Inhibitors (can increase levels of drugs it can interact with)	Inducers (can reduce levels of drugs they interact with)	Increased sensitivity to drugs
Cimetidine Ciprofloxacin Erythromycin COC's Ketoconazole	Phenytoin Carbamazepine Phenobarbitone Primidone Rifampicin → Will see increased GGT for patients on inducers ***	- Affect clotting/bleeding (reduced clotting factor 2,7,10) - Affect CNS (hepatic encephalopathy) - Diuretics – one of the risk factor is hypovolemia and reduction in K+ and Na+ - Constipation (increased risk of hepatic encephalopathy) – bc slow gut mobility mean nitrogenous waste in gut for longer for greater absorption
CCF Cirrhosis Viral infections	Smokers Heavy drinkers	

From WS 1 on Liver

POINT 1: confusion is symptom of alcohol withdrawal, HE, W-K syndrome

*** Liver receives 75% of blood from haptic portal vein, normally uninterrupted blood flow, however with damaged liver vascular resistance is increased due to fibrosis with formation of new blood vessels.

Impaired liver:

- 1> Reduced or cannot produce clotting factors 2,7,10 – increased PT, easy bleeding, bruising (VitK)
- 2> Impaired metabolism
 - i. Cannot conjugate & excrete bilirubin – Jaundice, increased ALP
 - ii. Cannot metabolise aldosterone (ascites)
- 3> No production of albumin – reduced osmotic pressure results in oedema (specially abdomen - ascites, due to portal HT)
- 4> Portal HT – collateral circulation (ascites, and Bleeding Oesophageal Varices)
- 5> Cannot excrete ammonia – failure to convert to urea for excretion (BBB HE)
- 6> Decreased haemoglobin levels – anaemia - bone marrow suppression at end stage
- 7> Increased ALT, AST, GGT – show liver cell damage

If patient had signs of liver disease but LTFs not raised – sever liver impairment where there are no hepatocytes left to produce enzymes so appear normal

POINT 2: Acute alcohol withdrawal – diazepam 10mg PO STAT

- Check symptoms + use clinical institute withdrawal assessment of alcohol scale (CIWA-Ar)
- Patient drink 15 units/day score of >15 on severity of alcohol dependence questionnaire (SADQ) – use this to select dose of treatment
- Benzodiazepine to control psychomotor agitation

MANAGEMENT of Liver Disease -> 살빼고 술끊기

Complications	Understand	Treatment options	Counselling points
Cirrhosis and end stage liver disease		<ul style="list-style-type: none"> ▪ Diuretics to minimise water retention ▪ Beta blockers and vasoconstrictor medicines for varices ▪ Lactulose in hepatic encephalopathy to prevent build-up of ammonia 	<ul style="list-style-type: none"> ▪ Low protein and sodium diet ▪ Draining of ascites fluid by paracentesis ▪ Surgery to treat portal hypertension and minimise risk of bleeding ▪ Transplant
Acute alcohol withdrawal	<ul style="list-style-type: none"> ▪ Minor symptoms: CNS hyperactivity resulting in insomnia, tremulousness, mild anxiety, GI upset, headache, diaphoresis (excessive sweating), palpitations (24-48h) ▪ Seizures: convulsions usually occurring with 12-48h of last drink, chronic alcoholic -> can lead to delirium tremens ▪ Delirium tremens (DTs) 48-96h after last drink – hallucinations (resolved w/i 24-48h), disorientation, tachycardia, HT, hyperthermia, agitation, diaphoresis (can be fatal) ▪ Fluid and electrolyte abnormalities 	<ul style="list-style-type: none"> ▪ Benzodiazepines e.g., chlordiazepoxide, oxazepam (reducing regime over <9 days) <ul style="list-style-type: none"> ➔ Control psychomotor agitation + prevent more severity ➔ Lowest possible dose given to suppress symptom w/o sedation ➔ If seizure IV lorazepam ▪ IV fluids and nutritional supplementation – if fluid electrolyte abnormal 	<ul style="list-style-type: none"> ▪ First manage what brought them in ▪ Frequent clinical assessment including vital signs ▪ Do not send home with supply – will produce profound respiratory if OD + dependent if combined with alcohol, finish regime
Cholestasis Pruritis	<p>Severe itchiness associated w/ liver disease</p> <ul style="list-style-type: none"> - Caused by deposition of excess bile salts under the skin 	<ul style="list-style-type: none"> ▪ First line: colestyramine For symptom control, an ion exchange resin that binds to bile salts in the gut ▪ Antihistamines: non-sedating to avoid encephalopathy E.g., cetirizine or loratadine ▪ Calamine lotion/menthol in aqueous cream – cooling effect on the skin 	
Ascites	<p>One of the most common complications and 50% patient w/i 10 years of chronic liver disease diagnosis</p> <p>Cause 1 activation of renin-angiotensin system due to reduction in renal blood flow from damaged liver (less urea production)</p> <ul style="list-style-type: none"> - End up with secondary hyperaldosteronism (increased aldosterone) -> cause fluid retention - Exaggerated by liver that can no longer metabolise aldosterone <p>Cause 2 reduction in the albumin production – reduces osmotic pressure in the plasma and causes oedema or fluid accumulation in tissues</p> <ul style="list-style-type: none"> - Bc of portal hypertension occurs as complication tf, oedema fluid retention tends to localise in the abdomen 	<ul style="list-style-type: none"> - We want to mobilise the abdominal fluid ▪ Diuretics: First line – spironolactone (aldosterone antagonist) Add on – furosemide (if no weight loss or peripheral oedema) ▪ Sodium and fluid restriction ▪ Paracentesis – physical removal draining of the fluid – Last resort ▪ Bed rest 	<p>Therapeutic monitoring parameter:</p> <ul style="list-style-type: none"> - Aim 0.5-0.75kg/day, if peripheral oedema 1-1.5kg/day <p>Toxic monitoring parameter:</p> <ul style="list-style-type: none"> - Too rapid loss of weight - End up risking hypovolaemia, hyponatraemia and hypokalaemia -> increased risk of encephalopathy
Wernicke- Korsakoff's syndrome	<p>Neurological abnormality due to thiamine deficiency</p> <ul style="list-style-type: none"> - Due to malnutrition from alcoholism - If left untreated can cause permanent brain damage 	<ul style="list-style-type: none"> ▪ IV Parbrinex (vit B/C preparation) TDS infusion over 30min for 3-5 days -> need facilities to treat possible anaphylaxis (toxic monitoring) ▪ Oral thiamine 100mg TDS administered together with IV then continued for 3-6 months or indefinitely -> to treat prophylaxis 	
Hepatic encephalopathy	<p>Due to ammonia and nitrogenous waste product from gut bypassing the liver and crosses the BBB</p>	<ul style="list-style-type: none"> ▪ Lactulose 30-50ml TDS (higher dose than constipation) – disaccharide molecule forming acid and reducing intestine pH ->1 ionisation of nitrogenous compound tf, reduction in ammonia absorption in gut ->2 alters intestinal flora tf, reduce ammonia producing bacteria ->3 speeds up gut transition time, leaving less time for ammonia to stay in the gut for absorption ▪ ADD ON: Rifaximin – semi synthetic derivative of rifamycin antibiotic ->Decrease production and absorption of gut ammonia ▪ If patient unable to take lactulose orally – Phosphate enemas ->Remove nitrogenous waste product from gut 	<p>Therapeutic monitoring: aim 2-3 soft stools</p> <p>Toxic monitoring: Avoid precipitating factors: dehydration, hypokalemia, GI hemorrhage, CNS drugs, high dietary protein (increase nitrogenous waste), constipation</p>
Portal hypertension	<p>Reduction in blood flow through the liver cells and blood is diverted from the portal system to somewhere else forming collateral circulation</p> <ul style="list-style-type: none"> ➔ Could cause bleeding oesophageal varices 	<ul style="list-style-type: none"> - Goal: manage risk associated with bleed in collateral circulation by reducing portal HT - Aim: reduced portal HT + resting HR by 25% ▪ Propranolol – low dose titrates up slowly (bc undergoes extensive first pass metabolism) ▪ Other vasodilators e.g., nitrate (if beta blocker propranolol not effective) 	
Bleeding Oesophageal Varices	<p>Collateral system developed to compensate portal HT – very thin walls, liable to rupture in stomach and oesophagus area – haemorrhage</p> <ul style="list-style-type: none"> ➔ Mortality 50% with 1st bleed 	<ul style="list-style-type: none"> ▪ First line – Resuscitation & correct hypovolaemia (massive blood transfusion + IV fluids) ▪ First line – Vasoactive IV therapy e.g., vasopressin, terlipressin, octreotide ->cause vasoconstriction of collateral blood vessels and reduce portal BP ▪ Endoscope – to identify bleeding ▪ Techniques to control bleeding: Sclerotherapy e.g. ethanolamine, ligation/banding/balloon tamponade, TIPS (transjugular intrahepatic portal systemic shunt) 	
Clotting abnormalities	<p>Develop in 75% of chronic liver disease patients – reduction in clotting factors (2,7,10) production</p> <ul style="list-style-type: none"> - Develop anaemia (reduction in haemoglobin) + increased bleeding and bruising 	<ul style="list-style-type: none"> ▪ PT >18 seconds start treatment ▪ Phytomenadione IV (vitamin K) – may not work in severe liver disease where they cannot produce clotting factors ->Will be successful if consequence of cholestasis or lack of absorption of bile acid 	<ul style="list-style-type: none"> ▪ Avoid aspirin, NSAIDs, warfarin (anything that increase risk of bleeding)

Complication	Understand	Treatment Options
Drug induced hepatotoxicity	<p>**Drug history taking important bc many can cause liver injury</p> <ul style="list-style-type: none"> - 20-40% all liver failure, 2-5% hospitalised jaundice, 10% acute hepatitis caused by drugs - Drugs withdrawn: troglitazone (antidiabetic), nefazodone (antipsychotic), ximelagatran (first alternative anticoagulant to warfarin) <p>Risk factors: age (young, sodium valproate for epilepsy, aspirin contraindicated under 16), sex (females more likely), alcohol, pre-existing liver disease, genetic factors, other comorbidities (HIV), drug formulation</p> <p>Drug toxicity mechanism:</p> <p>ADR Type A – intrinsic or predictable</p> <ul style="list-style-type: none"> ➔ Reproducible injury in animals, injury with dose, due to drug or metabolite, 80% of all ADR e.g., paracetamol or carbon tetrachloride <p>ADR Type B – idiosyncratic or unpredictable</p> <ul style="list-style-type: none"> ➔ Hypersensitivity or immunoallergenic e.g., phenytoin fever rash etc e.g., chlorpromazine or halothane, or metabolic idiosyncratic – indirect metabolite of offending drug 	<p>SIGNS (many drugs can cause inconsequential rise in LFT up to x2 upper reference)</p> <ul style="list-style-type: none"> - ALT more than double levels - Conjugated bilirubin more than double levels - Combined ALP and total bilirubin with one more than double levels <p>Other symptoms of liver disease discussed</p> <p>Management:</p> <ul style="list-style-type: none"> - Drug withdrawal - Antidote if appropriate e.g., paracetamol - Corticosteroids – used if hepatotoxicity remains 6 months after discontinuation, or deterioration continues after 3 weeks - Supportive therapy e.g., liver failure – liver transplant - Yellow card report if classified as serious <p>Prevention:</p> <ul style="list-style-type: none"> - LFT monitoring, patient education on signs e.g., malaise, nausea, fever, abdominal discomfort, OTC paracetamol risk no more than 4g
Paracetamol overdose	<p>Accounts for more than 50 percent of acute liver failure</p> <ul style="list-style-type: none"> - More than 15g lead to fatal hepatic necrosis - More than 7.5g risk of severe liver damage - More than 5g requires hospital admission and observation ➔ Diagnosed with serum paracetamol concentration <p>PHASES: 12H after ingestion antidote becomes less effective</p> <ol style="list-style-type: none"> 1> 30min to 24H after ingestion – asymptomatic, anorexia, nausea, vomiting 2> 18-72H after ingestion – RUQ abdominal pain, anorexia, nausea, vomiting, oliguria (lack of urine production) 3> 72-96H after ingestion – continued symptoms, hepatic necrosis seen: jaundice, coagulopathy, hypoglycaemia, hepatic encephalopathy, acute renal failure, death 4> Recovery after 4 days to 3 weeks – complete resolution if survived phase 3 	<p>METABOLISM OF PARACETAMOL</p> <ul style="list-style-type: none"> - Majority 95% undergoes conjugation with glucuronide then excreted in urine - Some 5% undergo metabolism via NAPQI <ul style="list-style-type: none"> *At normal dose – conjugation with glutathione occurs *At overdose – it becomes toxic <p>-> glutathione stores become depleted allowing NAPQI to accumulate and bind directly to hepatocytes causing cell damage</p> <ul style="list-style-type: none"> • Acetylcysteine (IV) and methionine (oral for remote areas) replenish glutathione stores • N acetyl cysteine (most effective within 8H, after 12H less effective)

RENAL

Assessment of renal function			
Plasma sample test → Done multiple times	Creatinine clearance	By-product of protein excreted by kidney – with renal impairment, increased creatinine level (but other factors impact as well) Glomerular filtration rate (GFR) ~ CrCl (creatinine clearance) Cockcroft & Gault equation (used in practice) – age, weight, gender (limitation of assuming avg population, unsuitable for child, pregnancy, renal function assumed to be stable -> Normal CrCl = 120ml/min → If creatinine plasma level increased or creatinine clearance decreased – kidney impaired	
	eGFR	Estimated glomerular filtration rate (volume of fluid filtered from glomerular capillaries to bowman's capsule per unit of time) Use MDRD or CKI-EPI to calculate -> >90 normal (1), 60-89 mild (2), 45-59 (3a), 30-44 (3b), 15-29 severe (4), <15 end stage (5) → Lower the more damaged Individualised depending on personal BSA	
	Urea	Nitrogenous break down product of protein metabolism made in the liver excreted by kidney → If urea level high in plasma indicated renal impairment → >15mmol/l considered uraemia → Can be raised by dehydration, muscle injury, infection, haemorrhage, excess protein intake → Cause key symptoms of N&V or pruritus (itching skin)	
Urine test	Proteinuria	Microalbuminuria	Albumin is protein found in blood should not be in urine
	ACR	Albumin:Creatinine ratio	Ratio predict renal disease development and risk of adverse outcomes e.g. CKD progression, AKI development or CVD Divide albumin (mg) by creatinine (g) → Higher ACR means increased albumin level >70mg/mmol in non-diabetic >2.5mg/mmol in male and >3.5mg/mmol in female -> in diabetics -> lower boundaries bc patients with values higher than this we use ACEi and closely monitor renal function
	Haematuria	Blood in the urine – trying to look at cause of renal impairment	May need to conduct as prescribers, if working at GP or CP
	Osmolarity	High particle concentration = high osmolarity	Concentration of urine – can decide visibly, dark urine
	Specific gravity	Solute concentration, higher gravity = more solutes	

Drug handling in renal impairment			
Absorption (A)	Distribution (D)	Metabolism (M)	Excretion (E)

EX) Diabetic patient on metformin advised to avoid if eGFR less than 30 -> hold prescription

Classification of causes of renal disease		
Pre-renal	Intrinsic Renal Failure	Post Renal Failure

Acute Kidney Impairment

Diagnosed as AKI if:

- Serum creatinine rise greater than or equal to 26.5 umol/L within 48hours
- Serum creatinine rise greater than or equal to 1.5-fold from their baseline value which is known or presumed to have occurred within the last 7 days
- Urine output is less than 0.5ml/kg/hr for 6 hours

Stage 1 – 1.5 to 1.9 x baseline creatinine

Stage 2 – 2.0 to 2.9 x baseline creatinine

Stage 3 – 3.0 or more x baseline creatinine

Risk factors: diabetes, CKD, Previous AKI, Hepatic disease, Congestive cardiac failure (CCF) or

Peripheral vascular disease (PWD), elders

Causes

Symptoms

AKI Management			
	Understand	Treatment	Counselling
Step 1: Identify the Cause			
Step 2: Restore and maintain renal function			
Step 3 Other treatments			

Chronic Kidney Disease

CKD MANAGEMENT

Complications of CKD			
Complication	Understand	Treatment	Management + Counselling
1) Water and electrolyte balance			
2) Acidosis			
3) Muscle Dysfunction			
4) Uraemia			
5) Hypertension			
6) Renal Bone Disease			
7) Anaemia			

SOLID ORGAN TRANSPLANT

Types of transplant: heart, lungs, liver, pancreas, kidney, bowel, multi-visceral (intestine, liver, spleen, stomach)

Process: 1) Transplant assessment with MDT 2) On waiting list 3) test for exclusion criteria (e.g., patient life expectancy lower than 2 year), donor-recipient blood group, HLA compatibility***

Immune system is the biggest barrier – immunosuppression to prevent graft rejection (acute or chronic), but risks – S/E, infections, malignancy and post-transplant lymphoproliferative disease

HLA compatibility:

Types of graft	
Xenografts	
Autograft	
Isografts	
Allograft (common)	

Immunology	

T cell recognition of foreign graft	
Signal 1	Interaction between the T cell receptor and the antigen presented by the MHC
Signal 2	Co-stimulatory receptor/ligand interaction between the T cell and APC
Signal 3	Growth signals activating the cell cycle

Induction immunosuppressant: given straight after when graft rejection risk is highest			
Drugs	Drug Type	Monitoring Parameters	Counselling
Basiliximab	Monoclonal antibody acts at IL2 receptor (CD25 T cell must be activated) Cause T cell depletion	Therapeutic monitoring: Toxic monitoring:	
Alemtuzumab	Monoclonal antibody acts on CD52 cell Cause cell lysis and T cell depletion	Therapeutic monitoring: Toxic monitoring:	
Antithymocyte globulin (ATG)	IgG	Therapeutic monitoring: Toxic monitoring:	
Prednisolone (+maintenance)	Corticosteroids	Therapeutic monitoring: Toxic monitoring:	

Maintenance immunosuppressant			
Drugs	Drug Type	Monitoring Parameters	Counselling
Ciclosporin	Calcineurin inhibitors	Therapeutic monitoring: Toxic monitoring:	
Tacrolimus		Therapeutic monitoring: Toxic monitoring:	
Azathioprine	Antiproliferative drugs	Therapeutic monitoring: Toxic monitoring:	
Mycophenolic acid (MPA) Active component: mycophenolate mofetil (MMF)		Therapeutic monitoring: Toxic monitoring:	
Sirolimus	Inhibits rapamycin (mTOR)	Therapeutic monitoring: Toxic monitoring:	
Balatacept	Selective T cell co-stimulation	Therapeutic monitoring: Toxic monitoring:	

Solid Organ Transplant – General overview

Nicola Moore
Addenbrookes Hospital Teacher Practitioner

Learning objectives:

By the end of this screencast and workshop, you should be able to:

- List the types of grafts and state their tendency to initiate an immune response (likelihood to be rejected) from the recipient
- Briefly describe the basic mechanism of rejection, how this is managed and the associated benefits of this for the patient

* focus on solid organ transplant (not stem/bone marrow transplant)

Types of transplant

- Heart
- Lung
- Liver*
- Simultaneous Pancreas and Kidney transplant (SPK)*
- Pancreas*
- Kidney*
- Bowel*
- Multi-visceral* – intestine, liver, spleen, stomach

Transplants done at Addenbrookes hospital

*Undertaken at Addenbrookes Hospital

Where from?

Law around organ donation:

<https://www.youtube.com/watch?v=22JdKKPB3P4>

- Deceased donor
- Living donor (altruistic or directed)
 - Liver
 - Kidney
- Exclusion
 - protein CID
 - skin, other cancer, HIV
 - ↳ leads to others

Process

- Transplant assessment → last step of treating patient
 - MDT
- Waiting list
 - Exclusion criteria e.g. patient has other disease and life expectancy ↓ years
 - Donor-recipient blood group
 - HLA-compatibility (see later)
 - ↳ not everyone can donate to everyone bc of disparity - difference in genetics of organs
- WAIT.....

The IMMUNE SYSTEM is the biggest barrier to transplant - Immunosuppression

Aims of Solid Organ Transplant

- Increased life expectancy
- Increased QoL
- (Decreased financial implications)

Issue

- Recipient immune response

Solution

- IMMUNOSUPPRESSION
 - ↳ to prevent rejection

Aims of immunosuppression

- Prevent graft rejection (acute and chronic)
- Induction of Tolerance → body won't have force response toward it
- Risks of immunosuppression
 - Side effects
 - Infections
 - Malignancy
 - Post Transplant Lymphoproliferative Disease



Types of graft

The immune response to a graft depends partly on the genetic disparity between graft and host

- Xenografts – between different species = greatest immune response = rejection
- Autograft – from one part of the body to another on the same individual = No rejection → skin hair transplant
- Isografts – grafts between genetically identical individuals = no rejection
- Allograft – between members of the same species = varied response dependent on degree of histocompatibility of donor and recipient (but also type of organ)

↳ most commonly used

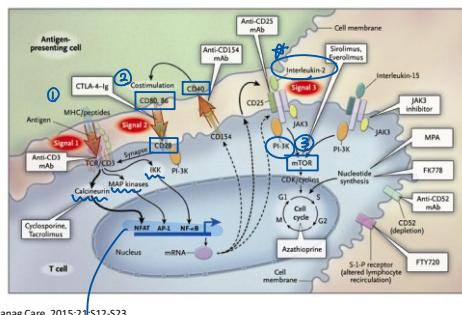
Immunology

- The antigens responsible for rejection are called **histocompatibility antigens** (products of the histocompatibility genes)
- The Loci of the genes eliciting the most vigorous rejection are those of the major histocompatibility complex - **MHC**
- In humans this is called the human leukocyte antigen **HLA**
- MHC are split into 2 classes - MHC I and MHC II
 - MHC I are normally expressed on all nucleated cells and present antigenic peptides from inside the cell to CD8 T cells
 - MHC II are only expressed on professional antigen-presenting cells, activated macrophages and B cells and present extracellular antigens to CD4 T cells
- Physiologic function - present antigen to T cells (as they only recognise it when in complex with MHC molecules)
- to present antigen to T cells*

Immunology

- Immune responses to transplants involve adaptive (both cellular and humoral response) and innate mechanisms *map here*
- T cells are central in the rejection of grafts. T cells become activated, undergo clonal expansion and differentiate to express effector functions.
- EXTREMELY** complex process – only covering the areas important in the understanding of the drug action
- Overall outcome of the immune response is injury/cell death to/in the transplanted organ – rejection

* Refer back when looking at drugs used in transplant



Am J Manag Care. 2015;21:S12-S23

How this T-cell is activated by APCs

HLA-compatibility = How does it work in transplant?

- There are ways in which we can minimise/control the host immune response
 - HLA compatibility → if organ incompatible to patient higher chance of rejection
 - Immunosuppression ✓
- MHC I partly encoded by genes at HLA-A, HLA-B and HLA-C loci
- MHC II encoded by genes in HLA-DP, -DQ or **-DR** region
needs to be matched
 - Strongest determinants = HLA-DR > HLA-B and HLA-A
 - Most important for matching
 - More than 1250 alleles determine these antigens

Explanation of diagram

- T cell recognition of foreign graft
 - Signal 1** – Interaction between the T cell receptor and the antigen presented by the MHC.
- Signal 2** – Co-stimulatory receptor/ligand interaction between the T cell and APC, i.e. CD28 of T cell and APC cell surface ligand B7-1 or B7-2 (aka CD80 and CD86). Another co-stimulatory interaction is CD40 with its ligand.
 - Activation of three signal transduction pathways
 - Calcium-calmodulin pathway
 - Mitogen-activated protein (MAP) kinase pathway
 - Protein kinase C-nuclear factor-kappaB
 - Responsible for transcription factor activation → *in itself activating response we see from T-cell*
- Signal 3** – Growth signals activating the cell cycle
 - Activation of the phosphoinositide-3-kinase (PI-3K) pathway and molecular-target-of-rapamycin (mTOR)

→ How effector functions T-cell is brought out.

→ Effector function: part of humoral immune response
essential link between innate & adaptive immunity

HLA-compatibility

- Benefits
 - Better graft function✓
 - Fewer episodes of rejection✓
 - Longer graft survival ✓ → *not much damage caused by rejection*
 - Possibility of reduced immunosuppression (potential for reduced infection and malignancy risk) *↓ amount / potency graft required*
 - Decreased risk of sensitisation increasing issues with further transplants if required
- May not be possible – therefore need protocol to overcome immunologic issues of mismatch
 - Least immunogenic mismatch
 - Immunosuppression

Immunosuppression

- There are two phases of immunosuppression – INDUCTION and MAINTENANCE
- ① • Induction
 - Corticosteroids
 - Basiliximab
 - Alemtuzumab
 - Antithymocyte globulin (ATG)

*↳ graft dysfunctioning
highest risk of graft rejection straight after.
enhanced by monoclonal, polyclonal antibodies
→ an expensive*
- ② • Maintenance
 - Ciclosporin / Tacrolimus – calcium channel inhibitor
 - Azathioprine / Mycophenolate – antiproliferative drug
 - Corticosteroids
 - Balatacept
 - Sirolimus mTOR inhibitor

1

Drugs at induction

- ① • Basiliximab – monoclonal antibody acts at IL2 Receptor
 - Chimeric (human/murine) monoclonal antibody against the IL-2 receptor (CD25) cells must be activated for this to be expressed)
 - Inhibits differentiation and proliferation but is minimally T cell depleting
 - Minimal adverse effects (no pre-med/specialist monitoring required)
 - Given at induction and 3-4 days post surgery
- ② • Alemtuzumab – monoclonal antibody acts on CD52 cell
 - Humanised, rat IgG monoclonal antibody directed against CD52 cell surface antigen causing cell lysis and prolonged depletion (also inhibits most monocytes, macrophages and natural killer cells) *of cells*
 - Associated with first dose reaction, neutropenia, anaemia, pancytopenia (rare) and autoimmunity (haemolytic anaemia, thrombocytopenia and hyperthyroidism)
 - Used to treat episodes of rejection

* extremely immunosuppressive :: Reduce need to start maintenance dose post surgery
→ could be beneficial

2

Drugs at induction

- (3) *use patients 1BW for doing to prevent excessive doing that lead to excessive side effects*
- Antithymocyte globulin (ATG) *less used regularly, more for rejection episodes*
 - IgG from horses or rabbits immunised with human thymocytes.
 - Blocks a large number of T cell membrane proteins (including CD2, CD3, CD45), causing altered function, lysis and prolonged T cell depletion *→ getting rid of those + causes ↑ those + causes*
 - Cell lysis can be responsible for cytokine release syndrome – fever, chills, hypotension
 - Associated with thrombocytopenia, leukopenia, occasional serum sickness and allergic reactions
 - Pre-medication – paracetamol, chlorphenamine and corticosteroid *↑ types hyper sensitivity reaction*
 - Close monitoring required *→ constantly*
 - Used to treat episodes of rejection – every 2 weeks
 - Corticosteroids (Review endocrinology notes from year 2)
 - Also used in maintenance therapy → given for months so more S/E
 - S/E: adrenal suppression, HTN, diabetes, osteoporosis, Cushing's syndrome, GI, Wt gain, hyperlipidaemia, infection, etc....

3



Drugs in maintenance - Calcineurin inhibitors

- (1) *use patients 1BW for doing to prevent excessive doing that lead to excessive side effects*
- Recipients generally remain on one of these for life
 - Ciclosporin
 - Is a metabolite of fungal, *Tolyphocladium inflatum*
 - Binds to cyclophilin (an immunophilin) to form a complex. Complex inhibits calcineurin phosphatase suppressing T cell activation by inhibiting cytokine production, primarily IL-2 *→ inhibit this enzyme → ↓ cell activation*
 - Concentration related adverse effects: nephrotoxicity, hypertension, if uncontrolled HT stop this therapy
 - Hyperlipidaemia, gingival hyperplasia, hirsutism, tremor
 - May also induce: haemolytic uraemic syndrome, diabetes mellitus (5% of patients)
 - Twice daily dosing regime (adjusted to levels) **measure patients creatinine & urea levels*
 - Therapeutic drug monitoring
 - Brand prescribing required – Neoral / generic *→ remain on brand – always prescribed as brand*
 - Metabolised by the CYP 450 enzymes = NUMEROUS interactions
 - Major positive impact on rejection and survival following transplant

100-300 µg / mL – trough level

4

↓
any inducer – e.g., rifampin, phenytoin, St John's wort, phenobarbital
→ will bring reduction in ciclosporin conc.
any inhibitors – e.g., clarithromycin, CCB – diltiazem, azel antifungals, ampravril, grapefruit juice
→ increase conc of ciclosporin

Drugs in maintenance - Calcineurin inhibitors

- (2) *use patients 1BW for doing to prevent excessive doing that lead to excessive side effects*
- Tacrolimus – most patients on the world
 - Macrolide antibiotic derived from *Streptomyces tsukubaensis*
 - Binds to FK506-binding protein 12 (an immunophilin) to inhibit calcineurin and T cell activation (binds a different intracellular protein to ciclosporin but has subsequent same mechanism of action)
 - More potent than ciclosporin →
 - Similar S/E to ciclosporin (nephrotoxicity and haemolytic uremic syndrome) but lower incidence of hypertension, hyperlipidaemia, hirsutism and gum hyperplasia and higher incidence of diabetes mellitus and neurotoxicity
 - Once or twice daily dependent on brand and transplant *e.g. renal transplant – once daily dose advargra MR*
 - Brand prescribing required – Prograf, Advagraf, Adoprot
 - Best absorption on an empty stomach (food decreases bioavailability) *liver transplant*
 - Therapeutic drug monitoring – trough level **BEARD KEP*
 - Metabolised by the CYP 450 enzymes = NUMEROUS interactions *– twice daily dose Adoprot*
 - Mechanism of action *same as ciclosporin*
 - Maintenance 1 mg/kg/day *5-50 µg/mL*

5

Drugs in maintenance - Calcineurin inhibitors

Important considerations for both drugs:

- Brand prescribing – inadvertent swapping caused toxicity and graft rejection
- Difference in bioavailability with different formulations
 - Oral cyclosporin dose approximately 3 times the IV dose
 - Oral dose of tacrolimus approximately 3-5 times the IV dose
- Ciclosporin has specific information regarding the dilution of the solution *J *swapping formulation needs checked*
- S/E more likely to occur above the therapeutic range but can be idiosyncratic and occur at normal concentrations
- Therapeutic drug monitoring
 - In hospital – daily 3/week once patients home
 - 3 months patients seen weekly
 - dose change – increase monitoring

6

↓
green blood test monitoring
and patients to report signs/symptoms

M180 screencast

Drugs in maintenance – Antiproliferative drugs

3

- Azathioprine
 - Please refer to RA lectures for MOA
 - Summary – 6-MP is converted to thioguanine nucleotides which interfere with DNA synthesis. Another metabolite can also inhibit purine synthesis.
 - Inhibiting proliferation of T and B cells
 - Main S/E: **Haematological** dose dependent myelosuppression can occur with over 50% of patients developing leukopenia – reversed by reducing/stopping the drug; thrombocytopenia (reversed by reducing/stopping the drug); N&V (alleviated when given with food or in divided doses)
 - Close FBC required → distinguish whether dose change
 - Once daily dosing ✓
 - Interaction ~~ALLOPURINOL~~ (reduce the azathioprine dose to 1/4)
 - reduce dose of 1/4
 - xanthine oxidase inhibitor.
 - important in break down of azathioprine

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- * function of thiopurine methyl transferase enzyme
 - in metabolism of azathioprine

Drugs in maintenance – mTOR

5

- Sirolimus
 - Used as an alternative to calcineurin inhibitors and antiproliferatives or in combination with calcineurin inhibitors
 - Formerly known as **rapamycin**, sirolimus is a drug that inhibits the mammalian target of rapamycin (mTOR)
 - Sirolimus firstly binds the immunophilin FKBP12 forming a complex that inhibits mTOR
 - mTOR is a serine/threonine protein kinase involved in regulation of cell growth, proliferation and of protein synthesis and ribosome biogenesis
 - Blockade of mTOR inhibits the cellular proliferation response to a variety of cytokines including IL-2

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Drugs in maintenance – Selective T cell co-stimulation blocker

6

- Balatacept → sometimes used as maintenance
 - Binds CD80 and CD86 receptors on the antigen presenting cell preventing CD28 on the T cell from binding → binds to costimulatory receptors CD80 CD86 & preventing CD28 on T cells from binding
 - Dosing divided into two phases:
 - Initial phase, IV day 1 and 5 and at the end of weeks 2, 4, 8 and 12
 - Maintenance phase, IV end of week 16 and every 4 weeks thereafter
 - Risk of post transplant lymphoproliferative disease
 - Used as an alternative to CNI
 - Comparison studies have shown equivalent patient and graft survival but a higher incidence of acute rejection

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- associated w/ B cells that have been infected by Epstein Barr virus
 - causes increased proliferation of these affected cells
 - immunosuppressed patients – don't get usual T-cell activation

Drugs in maintenance – Antiproliferative drugs

4

- Mycophenolic acid (MPA) is the active component of mycophenolate mofetil (MMF)
 - MPA blocks Inosine monophosphate dehydrogenase, the enzyme required for *de novo* synthesis of guanosine monophosphate nucleotides. This blocks purine synthesis preventing B and T cell proliferation
 - More potent than azathioprine with greater reduction in acute rejection
 - Main S/E: **Haematological** – neutropenia, leukopenia, mild anaemia; **Gastrointestinal** – diarrhoea can be dose limiting (EC MPA (Myfortic) may improve this)
 - Monitor FBC
 - Twice daily dosing
 - Important drug interactions
 - e.g. MMF level can be decreased by antacids, iron, rifampicin but can be increased by medications such as acyclovir, valacyclovir (antiviral)

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Drugs in maintenance – mTOR

• Sirolimus

- Therapeutic drug monitoring required maintenance level 12-20 µg/mL as trough levels
 - S/E:
 - Less nephrotoxic than CNIs : have glomerular effect and see proteinuria
 - Less likely to cause diabetes than CNIs
 - Risk of life threatening pneumonitis (resolves after treatment withdrawal)
 - Impair wound healing (mTOR inhibition of fibroblast response to fibroblast growth factor) – not used immediately post transplant
 - Hypertension, thrombocytopenia – haematox S/E don't just affect lymphocytes, but act on other rapidly dividing cells
 - Metabolised by the CYP 450 enzymes = NUMEROUS interactions with other rapidly dividing cells
 - Administer consistently (with or without food)

need wound to heal prior to starting this

X formulation

→ look at info, dissolved? fluids?

10

Drugs in maintenance

• Combination therapy

- As more therapy has become available the use of combination therapy with action at different sites has been shown to have better outcomes
 - Reduced steroid dose
 - Better patient outcomes – reduced rejection
- Dependent on type of transplant and perceived immunosuppressive challenge → some much higher chance of rejection – more potent used
- Initiated at the time of surgery
- Generally will have at least one continued life-long

i.e. e.g. at addenbrooke's

Renal transplant – Basiliximab (induction) + Advarage + Azathioprine/Mycophenolate + Prednisolone ↑↑↑

Small bowel – Alemtuzumab (induction) + Prograf + Mycophenolate + Prednisolone ↓↓↓

more potent

BD

more potent

immunosuppressive.

ulceration

Complications of immunosuppression

In addition to the individual side effect profiles....

• Infection → higher risk

- Pneumocystis jirovecii
- Cytomegalovirus
- Fungal infection, i.e. candida

) → immune supporting meds to prevent these from occurring

• Malignancy incidence of all malignancies is higher in immunosuppressed, those with a possible viral aetiology are very high, i.e. lymphoma due to Epstein Barr virus affects around 2%

of transplant patients

Supporting drugs steroids - GI disturbance
+ antifungals prescribed for ite.g.) some meds cause hypertension
statin + given

Functions → chronic kidney disease screens as ↑

- Excretory – Excrete waste products and drugs
 - Need to assess impairment, adjust doses, hold/stop nephrotoxics
- Regulatory – fluid volume and composition, bp, pH
- Endocrine – Erythropoietin production, renin production, prostaglandin production
- Metabolism – vitamin D metabolism



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Plasma Sample Test

Routine Tests

↗ more detail about ACR

Plasma	Urine
• Creatinine (by product of protein metabolism)	• Albumin : Creatinine ratio (ACR)
• Urea	• Osmolality - high particle concentration = high osmolality
• eGFR	• Specific gravity - solute concentration, higher gravity = more solutes Proteinuria/Microalbuminuria

done multiple times in hospital
→ to indicate renal function

concentration of urine - can be practically
→ dilute urine - dehydration

may need to conduct as prescribed,
if working at GP or community pharmacy

↑ product of protein excreted by kidney
with renal impairment - ↑ creatinine level
→ but other factors may ↑ creatinine as well

Creatinine Clearance

GFR (glomerular filtration rate) = CrCl (creatinine clearance)

- 24-hour urine collection

$$\text{CrCl (ml/min)} = \frac{\text{Urine Cr} [\mu\text{mol/l}] \times \text{Volume [ml]}}{\text{plasma Cr} [\mu\text{mol/l}] \times \text{Time}}$$

Time delays and suspect accuracy of urine collection

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if creatinine plasma level ↑ → kidney impairment
if creatinine clearance ↓ → kidney impairment

Creatinine Clearance

Cockcroft & Gault equation *Used in practice*

$$\text{CrCl [ml/min]} = \frac{[140 - \text{age}]}{\text{Plasma Cr} [\mu\text{mol/l}]} \times \frac{\text{Weight}}{\text{Age}} \times \frac{\text{Gender}}$$

*F = 1.23 males & 1.04 females

Limitations:

- Assumes average population data
- Unsuitable for children and pregnancy
- Renal function must be stable → assuming plasma creatinine is stable

Traditionally "normal" Cr = 55-125 µmol/l and "normal" CrCl = 120 ml/min

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↳ varies, just an idea

Creatinine clearance

GFR (glomerular filtration rate) = CrCl (creatinine clearance)

Question

Ms JL is an 80-year-old female admitted with a 3/7 history of diarrhoea and vomiting. You suspect she is in acute kidney failure and need to calculate her creatinine clearance. Her creatinine is 240 µmol/l and she is 65kg (IBW 57kg) and 5ft 5 inches.

Using the Cockcroft & Gault equation, what is her CrCl in ml/min, rounded to the nearest whole number?

$$\text{CrCl} = \frac{[140 - 80] \times 65 \times 1.04}{240}$$

$$= 16.9 \text{ ml/mm}$$

≈ 17 ml/mm *(given as whole number in practice)*

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→ measures how well your kidney is working
eGFR → estimated glomerular filtration rate

- Calculated using either:
 - MDRD - 4-variable Modification of Diet in Renal Disease equation
 - Serum Cr, age, sex, ethnic origin → some limitation as GA (cannot extrapolate to cover use children + pregnant patients)
 - Less accurate when >60ml/min/1.73m² and overestimates for elderly patients
 - CKI-EPI - Chronic Kidney Disease Epidemiology Collaboration Formula (most recommended)
 - Same limitations as CrCl
 - On-line calculator: www.renal.org/information-resources/the-uk-eckd-guide
 - Local laboratory calculations → not something we have to calculate
 - Race adjustment – Practice varies in x1.159 for Black ethnic groups → only in the US
 - 2021 – NICE removed this recommendation in their guidance and agreed that adjustment may not be valid or accurate (no definitive recommendation)

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$$BSA (m^2) = \sqrt{\frac{\text{height} \times \text{weight}}{3600}} \quad eGFR \rightarrow \text{lower the more damaged} \rightarrow \text{normalised body surface area}$$

Stage of renal impairment	eGFR (ml/min/1.73m ²)
Stage 1 (G1) – Normal GFR	>90
Stage 2 (G2) – Mild impairment	60-89
Stage 3A (G3a) – Mild to moderate	45-59
Stage 3B (G3b) – Moderate to severe	30-44
Stage 4 (G4) – Severe impairment	15-29
Stage 5 (G5) – Established/end stage	<15

GFR_{absolute} = eGFR x (individual BSA / 1.73) → can be individualised depending on personal BSA

[Prescribing in renal impairment](#) | Medicines guidance | BNF | NICE

↳ What goes into calculating someone's risk
↳ how it affects prescribing in practice

- nitrogenous breakdown product of protein metabolism
- excreted by kidney ∴ ↑ in this level suggest renal impairment

Urea

- Breakdown product of protein metabolism
 - >15mmol/l = uraemia (range: 1.7-6.7 mmol/l)
 - Can also be raised by
 - Dehydration
 - Muscle injury
 - Infection
 - Haemorrhage
 - Excess protein intake

urea level high in plasma
→ renal impairment

→ a factor where patient should start dialysis

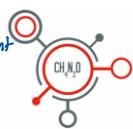
) : Never used in isolation
to diagnose renal impairment



CH3N4O2

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- can see key symptoms in chronic kidney disease
 - nausea & vomiting
 - pruritus : severe itching & irritation of skin



creatinine & urea → should be in urine & shouldn't be in blood → ∴ check plasma albumin → meant to be in blood & not in urine → ∴ check urine protein presence

Proteinuria / ACR

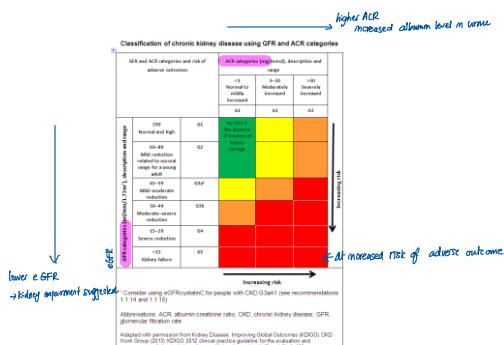
- Predictor of renal disease development & adverse outcomes
 - Albumin – protein found in the blood, should **not** be in the urine

- Albumin : Creatinine ratio (ACR) → Key indicator of

- Divide albumin (mg) by creatinine (g)
 - >70mg/mmol in non-diabetics
 - >2.5mg/mmol (M) & >3.5 (F) diabetics due to increased risk of developing renal disease

- ↑ a lot lower boundaries
- patient w/ values higher values than this → we use ACEi and closely monitor renal function
- risk is made to predict renal disease development & risk of adverse outcomes
e.g.) CKD progression, AKI development, CVD events

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17

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DRUG HANDLING IN RENAL DISEASE



ADME

- Absorption**
- Uraemia reduces drug absorption via: D&V, GI oedema
 - Reduced calcium absorption (less vitamin D activation) \rightarrow More m. CKD
 - Hyperphosphatemia - phosphate binder treatment reduces some drugs absorption \rightarrow In kidney impairment, body struggles to excrete phosphate \rightarrow phosphate level in blood

changes in degree of hydration
in kidney impaired patient due to fluid accumulation & fluctuation
 \therefore affect distribution of water soluble drugs in the body

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Urea competes w/ digoxin
↓ tissue binder
 \therefore ↑ digoxin serum concentration
 \rightarrow lead to adjust/reduce digoxin dose to avoid toxic accumulation.

- Distribution**
- Less protein binding (e.g. phenytoin due to hypoalbuminemia & urea)
 - Less tissue binding (e.g. digoxin, increased concentrations)

↑ urea is also a problem bc it competes w/ drugs for binding sites such as protein & tissue binding.
e.g.) phenytoin (highly protein bound drug \rightarrow albumin)
 \rightarrow urea competes w/ phenytoin for these binding sites
 \therefore ↑ free phenytoin level in blood
 \oplus if we have low levels of albumin in blood bc it leaves kidney (testing for it in urine where it shouldn't be)
 \rightarrow less albumin for phenytoin to bind

Ideal drugs in renal impairment

- Wide therapeutic index \rightarrow so action not tightly bound to small window
- Cleared by the liver \rightarrow unaffected by changes in renal function
- Not affected by fluid balance, protein binding or tissue binding \rightarrow unaffected by distribution factors.
- Not nephrotoxic

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Can be essential to use a nephrotoxic: \rightarrow due to co-morbidity, or has long term renal protective benefit e.g.) ACEI or ARB
Monitor renal function & toxicity.
In end-stage renal failure - no further renal function damage or decline. Monitor for toxic accumulation side effects.

not worried about nephrotoxic causing renal function damage but just worried about side effects + toxic accumulation

need to monitor renal function toxicity closely.

Question

50-year-old male with type 2 diabetes, prescribed metformin 500mg TDS. Admitted with eGFR=20ml/min/1.73m² (baseline eGFR=60).

Using the BNF only, what is immediate recommendation for the metformin prescription?

Metformin hydrochloride | Drugs | BNF | NICE

manufacturer advises to avoid if eGFR less than 30ml/min/1.73m²

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\therefore Hold prescription

What we would long dependent on patient renal function & blood glucose level \rightarrow if too high we need to find alternative.

\downarrow
won't be greatly affected
by avoiding 2-3 days of metformin

ADME

Metabolism \rightarrow ↓ less calcium absorption in Gut & Kidneys

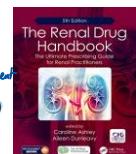
- Less vitamin D metabolism (less calcitriol production) = Less calcium absorption from gut and kidneys
- Less insulin metabolism in renal impairment \rightarrow type 1 diabetic insulin requirement affected
- Less elimination of pharmacologically active metabolites e.g., nor-pethidine
e.g.) morphine metabolite also accumulates causing toxicity
 \rightarrow alternate opioid cyclothiazide given
 \rightarrow bc less readily excreted.

Excretion

- Less excretion
- Dose adjustments: Lower dose and/or increased dose interval
- NO adjustment to LOADING DOSES
 \hookrightarrow not worried about distribution to the site of action - only maintenance dose allowed to avoid toxic accumulation.

for many drugs modification of dosing not necessary
however if drug eliminated by kidney - need to modify to avoid toxicity
 \rightarrow do this by reducing dose, increase dosing interval - end goal is to reduce total daily dose of the drug.

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Reference sources

- BNF/BNFC (CrCl/eGFR)
 - emc \rightarrow drug monographs - state what to do in renal impairment
 - Renal Drug Handbook / Renal Drug Database (CrCl)
- \hookrightarrow advise sources \hookrightarrow [CrCl ml/min]
 \hookrightarrow talking about CrCl

- CrCl (using IBW) should be used for obese patients (BMI > 30)
 \hookrightarrow If ABW < IBW then use ABW ideal body weight vs actual body weight

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CrCl = unit ml/min
eGFR = ml/min/1.73m² \rightarrow always check unit

drugs or anticoagulants - use ABW to calculate dose.

fate into consideration, the trend of their renal function & what we are using the drug for e.g.) if renal function on ↑ trend \rightarrow alter to higher dose side bc expect to carry on increasing or if using antibiotics - use higher dose to treat infection

Fill in the gaps

When adjusting drugs in renal impairment, you may need to either reduce the dose or increase the dosing interval.

An eGFR of 50 would describe a mild to moderate renal impairment (Stage 2A).

Uraemia can lead to symptoms including nausea and confusion as well as pruritis.

Glomerular filtration rate refers to the volume of fluid filtered from the glomerular capillaries into the Bowman's capsule per unit of time.

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\downarrow
if too high we need to find alternative.

CLASSIFICATION OF RENAL DISEASE & AKI

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Classification - Cause



1

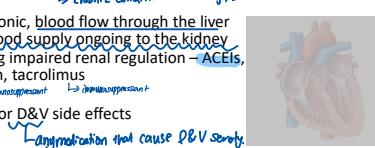
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PRE-RENAL

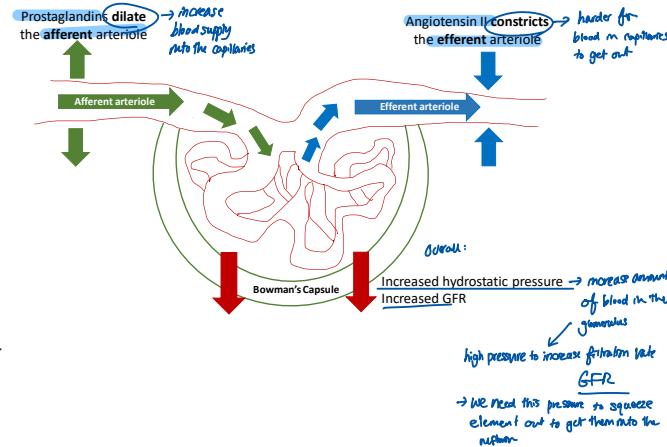
Pre-renal failure

(lack of blood supply to kidney)

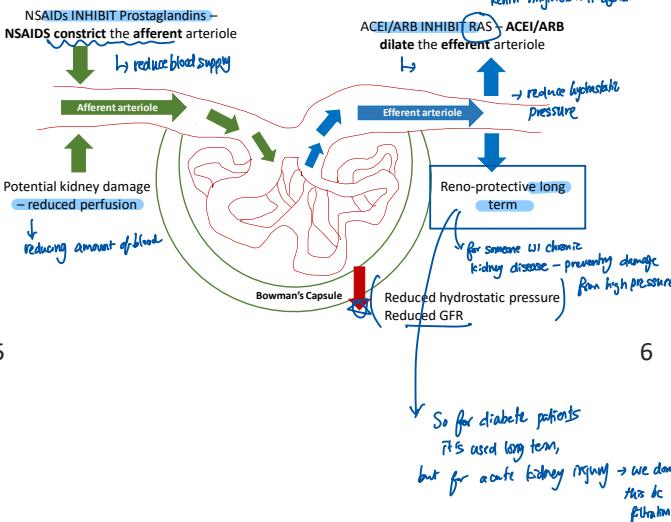
- Reduced renal perfusion
- For example ↑ low blood volume
 - Hypovolaemia (burns, dehydration, haemorrhage)
 - Reduced cardiac output – heart failure, MI → acute condition e.g. blood clot in lungs
 - Infection
 - Liver disease – chronic, blood flow through the liver reduces lack of blood supply ongoing to the kidney
 - Medication causing impaired renal regulation – ACEIs, NSAIDs, cyclosporine, tacrolimus
 - Diuretics → diuretic → dehydrates
 - Laxative abuse or D&V side effects
 - Angiotensin II causes P&V sensory → dehydration → hypovolaemic state



3

NSAIDs and ACEi in more detail:

4



Intrinsic Renal Failure

Intrinsic renal failure

→ damage to renal tissue

- Damage to renal tissue
- Can be secondary from pre-renal failure and prolonged reduced perfusion
- For example
 - Glomerular (e.g. diabetic nephropathy, glomerulonephritis)
 - Tubular (e.g. interstitial nephritis, acute tubular necrosis)
 - Renovascular (e.g. hypertension)
 - Infection
 - Nephrotoxicity – NSAIDs, Contrast media
 - Metabolic (e.g. hypercalcaemia, hyperuricaemia)
 - Congenital
- ↓ Intrinsic failure as a result of pre-renal cause
 - ↓ prolonged lack of blood supply & GFR → kidney tissue → causing necrosis of kidney tissue
- All inflammatory conditions can lead to ↓ afferent arteriole
 - Kidney is more vulnerable in these states to nephrotoxic medication that will further reduce perfusion e.g.) NSAID – ↓ afferent arteriole → ↓ hydrostatic pressure → ↓ GFR
- So painful can cause acute interstitial nephritis
 - Painful urine → increase renal function

5

6

1

Post Renal Failure

Intrinsic renal failure

Nephrotoxicity

Hypersensitivity reactions (unpredictable) Interpatient variability *

- Glomerulonephritis - Phenyltoin, penicillins not common but should be aware
- Interstitial damage - Penicillins, cephalosporins, allopurinol, azathioprine

Directly toxic (more predictable) * we know the drug is causative and contraindicated in certain renal stages

- Aminoglycosides, amphotericin, cyclosporin
- Can occur from a single dose

Vancomycin & gentamicin \rightarrow directly nephrotoxic

of monitoring culture

7

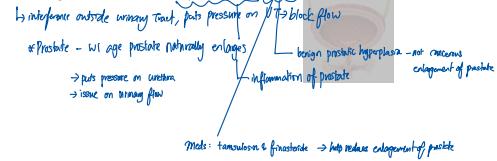


Post-renal failure

Obstruction to urinary flow \rightarrow cause back pressure into the kidney \rightarrow can cause damage & scarring

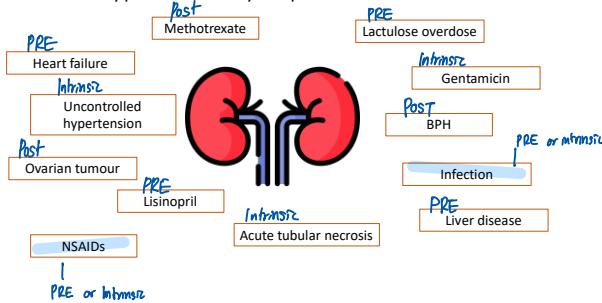
For example

- Stones blocking ureter (e.g. calcium oxalate)
- Structural (e.g. tumour, stricture) \rightarrow block urinary flow
- Nephrotoxicity (e.g. cytotoxic medication, high dose sulphonamides) \rightarrow cause depositions in urinary tract, block flora - create urate crystals
- Outside urinary tract (e.g. ovarian tumour, prostatitis, BPH)



8

What type of kidney impairment do I cause?



9

Classification - Reversibility



10

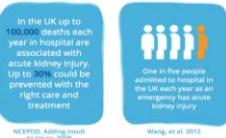
AKI on CKD (acute on chronic renal failure)

\rightarrow pre-existing chronic kidney disease $\&$ acute drop in renal function

AKI

Acute Kidney Injury (AKI)

Rapid decline (hours/days) in someone's usual level of kidney function, which has an up to 90% mortality rate if not identified and treated.



400-600 pts/million population/yr AKI

Up to 200 pts/million population/yr AKI require dialysis

Reversible

complete resolution

partial resolution

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Acute Kidney Injury (AKI)

Diagnosis of AKI

- ① Serum creatinine rises by $\geq 26.5 \mu\text{mol/L}$ within 48 hours or
- ② Serum creatinine rises by ≥ 1.5 fold from their baseline value, which is known or presumed to have occurred within the last 7 days or
- ③ Urine output is $< 0.5 \text{ ml/kg/hr}$ for 6 hours

\rightarrow hospital & care setting criteria

AKI staging example

- Stage 1 - 1.5 to 1.9 x baseline creatinine
- Stage 2 - 2.0 to 2.9 x baseline creatinine
- Stage 3 - 3.0 or more x baseline creatinine

higher the stage the worse kidney



flag patient in AKI on hospital chart
- high risk and high priority
- for med review

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STEP 2

AKI - Management

1 Identify the cause

- REMEMBER – Re-starting long term medication post-AKI is just as important as withholding in the short term. For example:

ACEI/ARB

- Preventing angiotensin-II mediated vasoconstriction of the efferent arteriole = vasodilation = reduced hydrostatic pressure and glomerular filtration rate
- Protective long term - prevent sustained vasoconstriction which leads stenosis of the efferent arterioles and loss of nephron function
 - \rightarrow prevent hypertension \downarrow sustained vasoconstriction \downarrow cause stenosis (narrowing) of efferent arteriole & loss of nephron function
- In AKI (hypovolaemic state) reduction of hydrostatic pressure worsens AKI – Hold until function improves

* In CKD - if some of the nephrons are out of action and putting more blood into nephron - can build glomerular pressure
 \rightarrow Used in CKD regardless of baseline function

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We don't want to reduce hydrostatic pressure we need to preserve filtration rate as much as possible \therefore hold drugs AKI

2 Restore and maintain renal function (volume status and BP)

- Aggressive, early fluid resuscitation to mimic the nature of fluid lost i.e. blood sodium chloride dehydration \rightarrow replace the fluid loss to build up the volume again
- Monitor input and output – if hypotensive we want positive fluid balance = more on
- Hypovolaemic – positive fluid balance to hydrate the patient and increase renal perfusion
- Dialysis can be used in ~1/3 patients to maintain renal function while treating the underlying cause (rapidly rising Cr/Urea, severe hyperkalaemia, metabolic acidosis)

\rightarrow late stage CKD patient
 \rightarrow in acute emergency setting
 \rightarrow rapidly rising creatinine levels
 \rightarrow severe hyperkalaemia – side effect of dialysis
 \rightarrow metabolic acidosis

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is helpful in protecting renal function & prevent steroids

AKI - Management

2 Restore and maintain renal function (volume status and BP)

- In fluid overloaded patients \rightarrow kidney stopped working not getting rid of fluid

Loop diuretics

- Only if no issue with renal perfusion – caution to avoid dehydration \rightarrow worsening of AKI
- Diuresis, reduced tubular cell metabolic demands, increase renal blood flow
- High doses: 1-2g IV over 24 hours (e.g.) furosemide
- 4mg/min max rate (higher risk of ototoxicity)

\rightarrow always hearing or balance problems due to a medicine

Dopamine – ITU

- Low dose 2mcg/kg/min = renal vasodilation through DA1 receptors increasing perfusion and urine output
- Higher dosing (>5 mcg/kg/min) can cause vasoconstriction

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Renal Perfusion: blood flow that passes through unit of renal tissue w.r.t. given time mL/mm²

STEP 3

AKI - Management

3 Other treatments

- Anti-biotics if infective cause (ensure appropriate dosing)

\rightarrow especially w/ IV – may need adjustment depending on renal function

\oplus AKI improvement, may need to alter dose of antibiotic daily depending on renal function

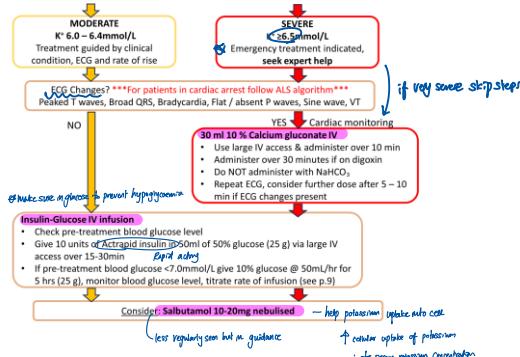
• Electrolyte correction - hyperkalaemia \rightarrow first possibility of AKI

- \ominus >6.5 mmol/L potassium = muscle weakness, ECG changes, v-fib, cardiac arrest \rightarrow cardiac side effects
- >6 mmol/L & AKI should be urgently treated in AKI patients
- Local guidelines – for AKI patients
- Protect the heart with calcium gluconate 10% IV (antagonises potassium) \rightarrow at coronary artery membranes
- Shift potassium into cells \rightarrow Rapid acting insulin in glucose over 15 minutes to stimulate sodium-potassium transporter and move K⁺ into cells
- Nebulised salbutamol - lower serum potassium levels by stimulating uptake into cells

\rightarrow to increase potassium uptake into the cells

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NAUH Hyperkalaemia Guideline



Resources

<https://www.thinkkidneys.nhs.uk/>
<https://www.thinkkidneys.nhs.uk/aki/resources/pharmacists/injury/thinkkidneys.nhs.uk/> - Medicines optimization toolkit \rightarrow daily used in practice
<https://www.cppc.ac.uk/therapeutics/aki>
<https://public.tableau.com/app/profile/ukkidney/vizzes>



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Fill in the gaps!

calcium channel inhibit antagonises potassium on cardiomyocyte membranes, thereby protecting the heart from arrhythmias.

Hyperkalaemia can cause dangerous symptoms such as ECG changes, ventricular fibrillation and cardiac arrest.

ACEI/ARBs cause vasodilation of the efferent arteriole, which decrease hydrostatic pressure and GFR. This is protective long term by preventing sustained vasconstriction, which leads to stasis of the efferent arteriole. This is damaging in AKI due to the reduction in hydrostatic pressure.

The 'triple whammy' of AKI medication is ACEI/ ARB, diuretics and NSAIDs.

CHRONIC KIDNEY DISEASE

Amy Kirkham
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Norfolk & Norwich University Hospital / UEA

1

don't need to know for exams



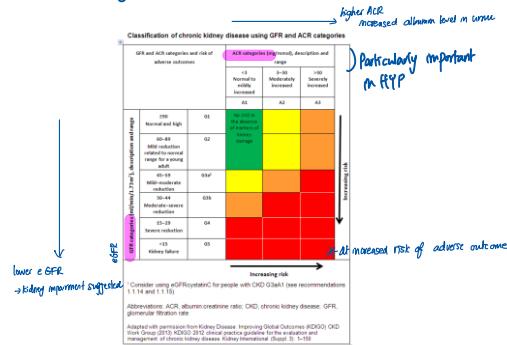
CKD

- Worsening, progressive and irreversible loss of kidney function
- Can lead to end stage kidney failure – permanent damage/loss of function
- UKKA – A patient with abnormalities of kidney function or structure present for more than 3 months.
- The definition includes all individuals with markers of kidney damage* or those with an eGFR of less than $60 \text{ ml/min}/1.73\text{m}^2$ on at least 2 occasions 90 days apart (with or without markers of kidney damage)

2

*Markers of kidney disease may include: albuminuria (ACR $> 3 \text{ mg/mmol}$), haematuria (or presumed or confirmed renal origin), electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy) or a history of kidney transplantation

Prescribing in renal impairment BNF:



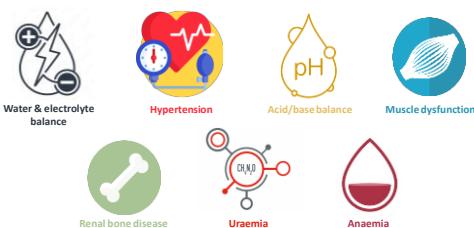
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CKD - Cause

- AKI – irreversible intrinsic damage
- HYP ← HTN – vessel thickening and narrowing leading to less blood flow (RAS system worsens and can cause glomerulosclerosis) → of the efferent arteriole
- Diabetes – nephropathy leading to fibrosis, membrane thickening and sclerosis
- Glomerulopathies/vasculitis/polycystic kidney disease
- ↓ blood vessel inflammation
- cause filtration to be altered or repaired
- Kidney sclerosis
- ↓ Hardening of kidney tissue
- blood flow will be directed to nephrons still working (compensate)
- More nephrons per kidney → hyperfiltration in those
- loss of more nephrons due to large workload

4

Complications of CKD



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Even with end stage kidney failure needing dialysis these complications are not resolved ∴ need management

① WATER & ELECTROLYTE

Inability to regulate water / electrolytes

- Early stages:
 - Polyuria/nocturia
 - Osmotic effect of urea ($> 40 \text{ mmol/l}$) → more dilute urine
 - Loss of ability to concentrate urine → more dilute urine
- CKD progression:
 - Then we see fluid retention – filtration rate of kidney starts to drop – patient cannot excrete sodium & water
 - Kidneys unable to excrete Na^+ & water
 - Peripheral & pulmonary oedema
 - Ascites
 - 80% have volume dependent HTN
- K+
 - Hyperkalaemia – kidneys inability to excrete, risk of cardiac arrest & ventricular fibrillation
- Acidosis – inability to remove H^+ ions = reduced bicarbonate levels
 - patient struggle to manage blood pH balance

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* for acute treatment : • calcium gluconate 10%
• insulin

Inability to regulate water – How do we treat it?

Fluid restriction - turn off the tap - less intake of fluid

hemodialysis → (HD not passing urine may be a lot less) $\rightarrow 500\text{mL/day}$

- Sodium restriction – dietary measures

Diuretics – take the plug out – prescription

- If fluid restriction alone does not achieve optimal dry weight
- Diuretics – Loop diuretics 1st line (**furosemide** up to 2g daily), **bumetanide** better absorbed if a lot of fluid accumulation in the abdomen \hookrightarrow preferred choice if fluid retention
- Metolazone** – cautious addition as a very strong diuretic, closely monitor \downarrow potassium levels \downarrow potassium levels

Monitor – daily weights at home & blood pressure

7 * in general we stop diuretics when dialysis starts

Inability to regulate electrolytes – How do we treat it?

• Potassium (**target 4.0-6.0mmol/L pre-dialysis in HD patients**)

- Acute management in screencast 2

• Medication review – medications / fluids contributing \rightarrow e.g.) ACE2 & ARB - more potassium, longer to act on those targets

• Long term management additional potassium binder

- Calcium res尼姆** – binds to potassium in the GI tract \hookrightarrow combat constipation side effect

• Releases calcium ions in exchange & constipation side effect – prescribed lactulose alongside

• 2019: **sodium zirconium cyclosilicate** and **patiromer calcium** approved by NICE for acute and chronic hyperkalaemia meeting certain criteria

• Allow CKD patients to stay on ACE/ARB for longer or at a higher dose

• Better adherence \downarrow total potassium levels

• Acidosis – Sodium bicarbonate PO 500mg TDS

metabolic acidosis

(2) Acid

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(5) HYPERTENSION

Hypertension

) can also cause of CKD
if blood vessel thickening
or narrowing

for result of CKD:

• Circulatory volume expansion due to sodium & water retention \rightarrow fluid overload \rightarrow volume expansion – volume dependent HYP

• Leads to artery stenosis = renin release = hypertension increases and increased rate of renal function decline

• Proteinuria

• Sustained HTN can lead to protein in the urine

• $>2\text{g}$ in 24hr = glomerular disease

• $>5\text{g}$ in 24hrs = severe disease (nephrotic syndrome)

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Know for Exams

Hypertension – How do we manage it?

Allison, caspase info

• Targets as per NICE guidance in all stages of CKD

- Proteinuria low (ACR < 70 or PCR < 100) – Target blood pressure < 140/90 mmHg
- Proteinuria high (ACR > 70 or PCR > 100) – Target blood pressure < 130/80 mmHg \rightarrow shorter, in with higher albumin creatinine ratio, patients more at risk of adverse outcomes

depends on
presence of
diabetes

- Encourage ACR testing to identify CKD earlier and ensure appropriate intervention

Hypertension – How do we manage it?

• CKD, HTN and ACR of 30mg/mmol or less – NICE hypertension guidelines

• Don't forget lifestyle measures!

<https://www.nice.org.uk/guidance/ng136/resources/visual-summary-pdf-6809910517>

• CKD, HTN and ACR > 30mg/mmol OR diabetes and ACR is 3mg/mmol or more

• ACEI/ARB started and optimised

• ACEI/ARB may be also be offered to CKD patients who do not have existing hypertension or diabetes if ACR is 70 mg/mmol or more

\hookrightarrow blood pressure fine, not diabetic \rightarrow but ACR > 70mg/mmol \Rightarrow ACEI/ARB

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Hypertension – How do we manage it?

• ACEI/ARBs

- **Monitor potassium** prior to treatment & 1-2 weeks after initiation/dose change → to reduce side effects of hyperkalaemia
 - Potassium binder may be required if hyperkalaemia on repeat sample
- **Creatinine monitoring** - 1-2 weeks after initiation/dose incrementation → at end stage, we don't worry about effects of these drugs on creatinine → more concerned with baseline parameters of potassium

CONTRA-INDICATION in renal artery stenosis

- Thickening blocking of arteries*
- Atherosclerosis in renal arteries supplying blood to the kidney = reduced GFR due to reduced perfusion
 - RAS system constricts the efferent arteriole to maintain pressure & perfusion
 - RAS blockers (ACEI/ARB) block this compensatory mechanism → chronic loss of perfusion
 - Relying of RAS to constrict efferent arteriole to maintain pressure in the glomerulus

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Hypertension – How do we manage it?

Other Hypertensives used:

- CCBs – ankle oedema (side effect from CCB, especially nifedipine)
 - CKD patients known to have resistance HYP
- Diuretics – not usually for HTN, mainly oedema
 - Thiazide diuretics (except metolazone) ineffective CrCl <25ml/min → will not work if renal function that impaired
 - Potassium sparing diuretics increase hyperkalaemia risk
- Beta blockers – cardio selective e.g. metoprolol (cleared by the liver), low dose and titrate but tend to use atenolol, bisoprolol because we are used to using them
- Alpha blockers – e.g. doxazosin, cleared via the liver
- Vasodilators – only if struggling to control with other agents → last resort because of side effects of reflex tachycardia (use with B-blockers), fluid retention (use with diuretics) and minoxidil causes excess hair growth

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SGLT2s

- Na⁺ glucose cotransporter in apical membrane → glucose efflux*
- Renal protective effect – key renal trials (CREDENCE, DAPA-CKD)
 - Mechanism unknown → slow progression of CKD and reduce adverse outcomes
 - Proposed via inhibiting sodium reabsorption this activates adenosine = vasoconstriction of the afferent arteriole (tubuloglomerular feedback)
 - Prevents prolonged high pressure and damage in the glomerulus
 - **Dapagliflozin is the only licensed currently for CKD**
 - Add-on to optimised standard care including highest tolerated ACEI or ARB unless contraindicated
 - eGFR 25-75ml/min 1.37m² at the start of treatment with T2DM or uACR of atleast 22.66mg/mmol

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SGLT2s

• Warnings/education

- Sick day rules – held when acutely unwell particularly in dehydration or acute hospital admission
- MHRA warning – DKA that can be euglycemic
- MHRA warning – Fournier's Gangrene

*held to prevent DKA
(diabetic ketoacidosis)*

*patient can be in DKA, but presents normal blood glucose
∴ need to monitor ketones*

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⑥ Renal Bone Disease

Renal Bone Disease → occurs in CKD stage 4 & 5

↑ Hyperphosphataemia

- Less excretion of phosphate by the kidneys = build up in the blood
- Symptoms include pruritis → itchy and irritation of skin

↓ Low Vitamin D

- Less activation of vitamin D → active vit D
 - Cholecalciferol converted to calcitriol by hydroxylation in 25 position in the liver and 1alpha position in the kidney (2nd step impaired)
- = defective bone mineralisation & osteomalacia (bone softening)

Renal Bone disease

Hypocalcaemia → main cause of low calcium

- Less vitamin D = less absorption of Ca from GI tract and kidneys
- More phosphate = more sequestering of calcium as calcium phosphate in bones → secondary pain

✗ 3 blood Test Pillars.

Phosphate · Vit D · Calcium

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Parathyroid gland sit on thyroid
→ detect low level of calcium in blood (hypocalcaemia)

→ release PTH into body

→ increase reabsorption of calcium and phosphate

- via kidney (not working in CKD)

- via bone

↓ increase in bone turnover

- combat low calcium levels in blood

• Increased bone turnover to release calcium into the bloodstream

• Weakening on the bone architecture

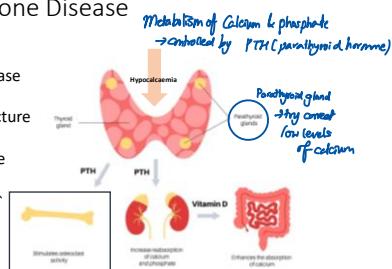
① (osteitis)

• Osteopenia and osteoporosis are common ②

• Increased fracture risk ③

• Bone hardening (osteosclerosis)

Renal Bone Disease



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secondary hyperparathyroidism
- tries to combat low levels of calcium
- but doesn't work
- becomes enlarged, overworked



Renal bone disease – How do we treat it?

- Hyperparathyroidism**
- Manage calcium
 - Manage phosphate → prevent 2nd parathyroid diseases
 - Effective management of the previous
 - Parathyroidectomy
 - Cinacalcet – lowers PTH levels by increasing sensitivity of calcium receptors (calcimimetic) → tricks the body – lower PTH levels in body
 - Paricalcitol – IV Vitamin D analogue (expensive)

LAST RESORT : Remove parathyroid glands

20

Renal bone disease – How do we treat it?

Hyperphosphatemia

- Diet – phosphate intake
 - 1st line
 - Bind with phosphate in the gut (take with/before meal and dose accordingly)
- High adherence issues – large tablets/tablet burden/GI side effects
 - Always check before changing drugs

Hypocalcaemia & low vitamin D

- Vitamin D3 analogue e.g. calcitriol (activate), alfacalcidol (activated in the liver)

Calcitriol – deactivated vit D3 not this

Learn these

Renal bone disease – What are the targets?

- Targets vary depending on CKD stage, dialysis & the unit
- PTH: >2x and <4x upper limit of normal
 - Phosphate: 1.1-1.5mmol/l (1.1-1.7mmol in dialysis)
 - Calcium (corrected): 2.2-2.6mmol/l

40.53

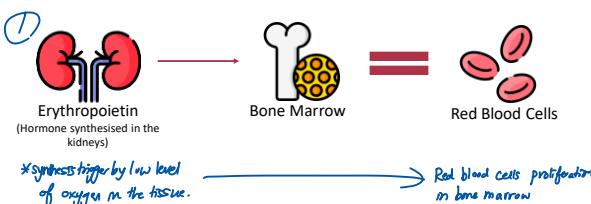
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7) Anaemia

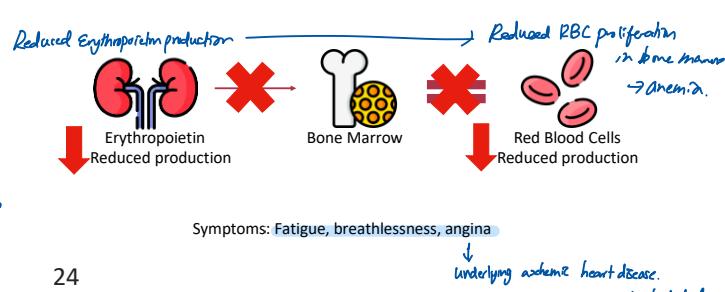
Common from CKD stage 3

Renal anaemia



23

* synthesis triggered by low level of oxygen in the tissue.
* more red blood cells – more oxygen transport
.. solving problems of hypoxia



24

↓ underlying anaemia heart disease
→ patient experience angina due to lack of O₂ delivery

Renal anaemia – How do we treat?

Replace erythropoietins by IV/SC

- Recombinant human erythropoietins by injection (IV/SC)
 - Epoetin alfa [Eprex®], Darbepoetin [Aranesp®], Epoetin beta [NeoRecormon®]
 - Side effects – HTN, pre red cell aplasia (Eprex® only)
- Hypoxia-inducible factor*
 - HIF stabilisers – Roxadustat - involved in gene expression in erythropoiesis to increase Hb production and improve iron response
- **Hb target: 100-120g/L**
 - regardless of CKD stages, dialysis.*

*Known as
Epo injection*

Renal anaemia

(2)

- Iron deficiency – reduced absorption ability
- Need sufficient stores for erythropoietin treatment to be effective
- **Target ferritin range: 200-500mcg/L** (Max 800mcg/L and minimum >100mcg/L)
- PO iron may be sufficient for pre-dialysis patients
- Most patients will need **IV replacement** e.g. Ferinject®, Venofer®
 - Serum ferritin <200mcg/L
- **AVOID blood transfusions** – renal transplantation in the future

Epo → work to stimulate RBC production

** need enough iron in
body to bring about
the co-transport RBC*

*IRON REPLACEMENT
FIRST*

*↓
increase chance of rejecting the graft*

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Complications of CKD

- Vitamins
 - Renavit – contains water soluble vitamins alongside dietary advice
 - Particularly on dialysis as removes water soluble vitamins
- Hepatitis B vaccination
 - 5 yearly booster for all CKD patients with blood manipulation, particularly haemodialysis (monitored yearly for antibodies)
 - Doses are doubled at 3x 40mcg doses



Which drug?

- ✗ ACEI / ARB
 - ✓ Calcium Channel blockers
 - ✗ Thiazide Diuretics (not metolazone)
 - Dapagliflozin
 - Sevelamer
 - Cinacalcet
 - Eprex®
1. Calcimimetic which lowers PTH levels
 2. MHRA warnings of DKA and Fournier's Gangrene, and sick day rules must be followed
 3. Have a side effect of ankle oedema
 4. Phosphate binder
 5. May need to be given after Ferrinjection to boost iron stores
 6. Contraindicated in renal artery stenosis
 7. Ineffective when CrCl <25ml/min

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When do we initiate dialysis?

- ESRF (average GFR 7ml/min)
 - Becomes unmanageable by other intervention
 - Symptoms: Extreme fatigue / lethargy, N&V, itching, drowsy, bone pain, inability to urinate, weight loss
 - Joint decision between MDT and the patient
 - Ultimately patient choice & may not be suitable
 - Life-lengthening but not curative
- Some not suitable for dialysis : some elderly that are too fragile for these interventions and would be a sacrifice for their quality of life*



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Dialysis principles

1. Mimicking the glomerulus

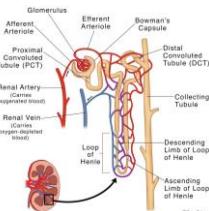
Ultra-filtration

① Remove fluid fluid
Remove fluid - hydrostatic pressure or osmotic gradient
Waste product removal – diffusion from high to low concentration across a semi-permeable membrane

② Remove waste waste
not the reabsorption
Mimicking the proximal/distal convoluted tubule and Loop of Henle

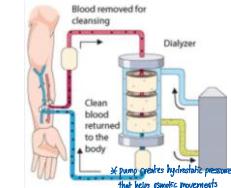
Reabsorption / conservation of wanted molecules
Dialysate fluid composition tailored to the patient's biochemistry

→ encourage reabsorption and conservation of certain molecules



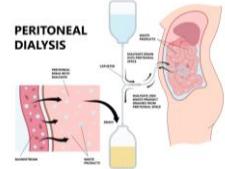
Dialysis

HAEMODIALYSIS



Artificial kidney. Hollow fibres create a semi-permeable membrane for diffusion

→ take blood from the body into a separate machine that has an artificial kidney inside



Patient's own peritoneum acts to mimic the glomerular basement membrane.

Is blood rich, and we for the peritoneal space w/ dialysate fluid to allow exchanges to occur

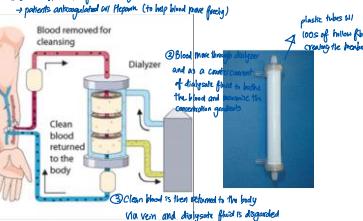
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Here using a filter called dialyzer to clean the blood
→ acts as an artificial kidney

Haemodialysis

① arterial blood taken from the body
→ patients anticoagulated w/ heparin (to help blood pass freely)



Haemodialysis

• Need direct access to the blood stream with strong flow

• Temporary catheter (emergent access) into the internal jugular vein / femoral vein → infection / thrombosis risk + blood clot risk

• Gold standard – arteriovenous fistula

→ Joined artery and vein together to create two large vessels

• Lasts a lot longer, lower risk of infection and clotting

• Placed under local/general anaesthesia, radial or brachial artery

• Takes 6-8 weeks to mature

6-8 weeks before dialysis start



5

6

join thick walled artery to a thin walled vein
→ over 6-8 weeks vein thickens up and enlarges
→ now two large vessels we can connect for dialysis

Need to keep the area protected
- clean, covered, keeping from contact or injury

Dialysis adequacy

- How well toxins and waste products are being removed from the patients' blood
 - Increased adequacy by:
 - Increase blood flow rate
 - Increased size/surface of dialyser
 - Longer on dialysis / more frequent
- total patient's wellbeing and safety is key!
 → monitor patient's bloodchemistry and weight to ensure the sessions are effective and optimised
 e.g.) fluid removal - monitor patients weight, before & after dialysis
 → make sure we are not overloading the muscle fluid or one go.
 → cause side effects like dizziness & hypertension
 → When a patient starts dialysis, we tend to load them up to an appropriate length of session to prevent disequilibrium syndrome
 Ureaemia → urine : may even cause constipation
 3hrs x 3 / week
 mon. week fri

7

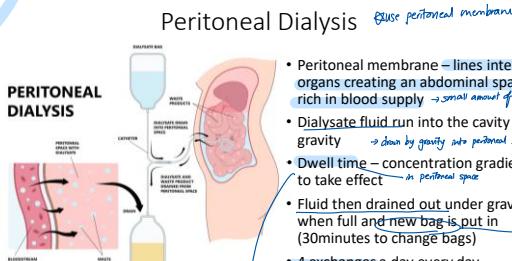
Dialysis adequacy

- Work up to 3-5 hours to prevent disequilibrium syndrome: headaches, N&V, convulsions in large urea removal
- Usually, 4 hrs 3x weekly
- Assess wellbeing, fluid status and lab parameters
 - Assess weight before and after dialysis
 - Tolerance - dizziness, hypotension
 - Fluid accumulation between sessions - max 1.5 kg gain & each patient has a tailored 'dry weight'

8

- ~~Excess peritoneal membrane~~
- No more than 1.5 kg gain → put at risk of pulmonary oedema
 - Tailored dry weight → acute hospital admission for cardiac failure from fluid gain.

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- Peritoneal membrane - lines internal organs creating an abdominal space, rich in blood supply → small amount of fluid, but generally empty space.
- Dialysate fluid run into the cavity by gravity → down by gravity into peritoneal space.
- Dwell time - concentration gradient to take effect → in peritoneal space
- Fluid then drained out under gravity, when full and new bag is put in (30 minutes to change bags) → drainage bag
- 4 exchanges a day every day → connected on aseptic techniques for often changing lines/bags
- At home
 - patient can do at home, give independence
 - mouth supply given to do at home
- try to use high glucose concentrate solution so that fluid goes out via osmosis into the dialysate fluid → creating an osmotic gradient for fluid removal by using high glucose content solutions



Types of peritoneal dialysis

4 exchanges at home / day

- Continuous ambulatory peritoneal dialysis (CAPD) already discussed
- Automated peritoneal dialysis
 - Exchanges carried out via a machine overnight over 8-10 hours
 - 1-3L drained into peritoneum ~~every 1-5 mins~~
 - Dwells for 1-3 hours then replaced
 - Reduced peritonitis incidence
 - More frequent and shorter dwell times so improved dialysis adequacy

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Peritoneal dialysis - Access

- Indwelling Tenckhoff catheter
- Inserted under ~~local/general anaesthetic~~
- Through the abdominal wall and sits in the cavity
- Cuffs and stitched on either side of the abdominal wall to hold in place - scar tissue will form and become watertight over time
- Clean technique required on changing catheter lines



between the umbilicus and through the abdominal wall → curly end to form the peritoneal space to deliver fluid

if patient will take prophylactic antibiotic daily to minimise infection
 it is not used for a couple of weeks and the exit site should be kept clean and dry

Peritoneal dialysis

Advantages	Disadvantages
Reduced anaemia as less loss of blood at needling sites	Risk of PD peritonitis (cloudy bag, IV → can lead to severe infection and loss of catheter) Vancomycin ← ciprofloxacin → removing from positive and grown negative
Less aggressive so does not leave patients as fatigued as HD	St in peritoneal space for hours Membrane can become fibrosed and inefficient
Better for cardiac stability - gentle rate of fluid removal	Risks of hypoglycaemia due to high glucose high glucose content solutions Risks of catheter blockage
Can be done at home, more independence	Requires a lot of equipment and good technique Incentive to hospital out
Dietary and fluid restrictions not as strict	Less clearance of smaller molecules e.g. urea, creatinine Compound to home analysis

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Diet & fluid

- Healthy diet – low fat & salt, high fibre
 - Low potassium – chocolate, potatoes, caffeine → many patients eat before dialysis because they know dialysis will be removing it for them
 - Low phosphate → lot of phosphate in our proteins
 - High protein in CAPD – can lose protein through CAPD fluid
- Contradicting need balance between the two*
- Haemodialysis – urine output + 500ml/day
 - Peritoneal dialysis – urine output + 750ml/day
- Fluid restriction from temp any liquid : gravy, icecream etc*
- ↓ Stomach w/ thirst quenching
↓ Reorder sucking (raise thirst but can spit out)*
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Medication considerations

CKD complications and how treatment may change

- Fluid management – stop diuretics unless residual function to pass urine
 - Acid/base balance – stop sodium bicarbonate *blood pressure*
 - Hypertension – monitor pre- and post-dialysis likely to reduce after dialysis, medical management still required
 - Renal bone disease – remain on treatment *haemodialysis → renal anaemia*
 - Erythropoietin – Risk of blood loss increased on dialysis so still required and usually given with IV iron on dialysis
- still needs to be medically managing, need to monitor pre+post dialysis
by removing a lot of fluid in dialysis = blood pressure likely lower post dialysis*

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Dialysis effect on drugs

Drug factors - increase likelihood of removal	Dialysis factors <i>↓ dialysis can also influence rate of drug removal</i>
Low molecular weight <i>↓ more likely to be removed</i> <i>e.g.: penicillins (77), vancomycin (100), gentamicin (50)</i>	Membrane type (HD)
Low plasma protein binding	Dialysis duration
Low volume of distribution	Fluid composition, concentrations and volume (osmotic concentration gradient PD)
High water solubility	Peritoneum pathology (PD) <i>↓ peritoneal - less efficient at remove</i>
High renal clearance in usual kidney function	Blood flow rate (HD) <i>↓ dialysis adequacy, remove rate, increase pressure</i>

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Renal Drug Handbook Dialysis effect on drugs

Pharmacokinetics

Molecular weight (daltons) Amoxicillin: 365.4; Clavulanic acid: 199.2
% Protein binding Amoxicillin: 20; Clavulanic acid: 25
% Excreted unchanged in urine Amoxicillin: 60; Clavulanic acid: 40
Volume of distribution (L/Kg) Amoxicillin: 0.3; Clavulanic acid: 0.3
Half-life - normal/ESRF (hrs) Amoxicillin: 1-1.5 / 7-20; Clavulanic acid: 1 / 3-4

Dose in patients undergoing renal replacement therapies

(peritoneal dialysis)
 HD/CAPD Dialyzed. Dose as in GFR<10 mL/min.
 (Haemodialysis)
 HD Dialyzed. Dose as in GFR<10 mL/min.
 Hemofiltration. Dialyzed. Dose as in GFR<10 mL/min.
 CVVHD. Dialyzed. Dose as in GFR<10-30 mL/min. See 'Other information'.

$$GFR = CrCl$$

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Fill in the gaps!

Dialysis aims to mimic ultra - filtration in the glomerulus and reabsorption in the proximal/distal tubules and Loop of Henle.

Haemodialysis uses a network of hollow fibres which act as a membrane between the blood and dialysate fluid. A pump in the machine generates a hydrostatic pressure which encourages fluid removal. Waste products move out of the blood by diffusion.

Drugs with low molecular weight, low plasma protein binding and low volume of distribution are more likely to be removed by dialysis.

A high blood flow rate, long duration of dialysis and the composition of the fluid used help to improve dialysis adequacy.

Dose in Renal Impairment

GFR (mL/min): 30-50

Dose as in normal renal function.

GFR (mL/min): 10-30

IV: 1.2 g every 12 hours.

Oral: Dose as in normal renal function.

GFR (mL/min): <10

IV: 1.2 g stat followed by 600 mg every 8 hours or 1.2 g every 12 hours.

Oral: Dose as in normal renal function.

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NEPHROTOXICITY

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Classification:

- Pre-renal
- Intra-renal
- Post-renal

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Pre-renal:

Under perfusion of kidney:

- Diuretics
- g.i.losses [D&V, laxative abuse]
- NSAIDs (Cyclooxygenase inhibition ⇒ inhibition of vasodilatory PGs)
- ACEIs

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Intra-renal:

Hypersensitivity reactions & unpredictable:

- Glomerular lesions [glomerulonephritis]:
 - eg. gold, penicillamine, phenytoin, penicillins
 - Passive trapping of immune complexes in glomerulus causing inflammatory response
- Interstitial damage [interstitial nephritis]
 - eg penicillins, cephalosporins, allopurinol, azathioprine
 - inflammation of cells lying between nephrons

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Directly toxic and more predictable:

- Eg aminoglycosides (damage proximal tubules), amphotericin, cyclosporin
- Can occur with a single dose

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Post-renal:

Due to urinary tract obstruction:

- Eg. high dose sulphonamides, methotrexate
- Causing crystalluria
- Crystals block outflow of urine ⇒ back pressure ⇒ damage/scarring to kidneys

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- Often essential to use nephrotoxic drugs in renal patients;
- ⇒ Constant monitoring of renal function and signs of toxicity
- ⇒ Once in ESRF, cannot cause any further renal damage or decline in renal function BUT patients will be at risk of other side-effects associated with toxic accumulation

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