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 hormonal effects, external compression, and intrinsic changes in the ureteral wall. Urinary frequency and nocturia are common, but usually require no specific treatment. Urinary incontinence also can occur during pregnancy. Other physiologic changes in pregnancy include: respiratory alkalosis, mild hyponatremia, glucosuria, and proteinuria up to 300 mg/day. Renin-angiotensin –aldosterone system Renin • Released by juxtaglomerular cells in kidney in response to ↓ renal perfusion, low sodium • Hydrolyses angiotensinogen to form angiotensin I • when decreased cardiac output occurs, stimulation of renin release is the primary event which leads to peripheral oedema • renin ↓in primary hyperaldosteronism due to negative feedback (↑ Aldosterone ↑ BP ↑renal perfusion ↓ renin) Which renal cells would respond first to this acute event of hypotension to increase blood pressure? Juxtaglomerular cells Factors stimulating renin secretion • ↓ BP → ↓ renal perfusion • Hyponatremia • renal artery stenosis • Sympathetic nerve stimulation • Catecholamines • Erect posture Factors reducing renin secretion • β-blockers • NSAIDS

Chapter 6

Nephrology Angiotensin • ACE in lung converts angiotensin I → angiotensin II • Vasoconstriction leads to raised BP Aldosterone • Released by the zona glomerulosa (the outer layer of adrenal cortex) in response to raised angiotensin II, potassium, and ACTH levels • Act in distal tubule retention of Na+ in exchange for K+/H+ : ↑ resorption of Na+ ↓Na+ loss in urine ↑ resorption of water (osmotic effect due to ↑ Na+) ↑ excretion of K+ The counter-current concentrating mechanism in the kidney Urine is concentrated by a complex interaction between the loops of Henle, the medullary interstitium, vasa recta and the collecting tubules, collectively termed 'the counter-current mechanism': • Vasa recta possess fenestrated walls that facilitate the movement of diffusible substances (free movement of water and electrolytes across the walls of the vasa recta) • Fine-tuning of the salt and water balance is achieved in the distal and collecting tubules under the influence of aldosterone and antidiuretic hormone • The ascending limb of the loop of Henle is impermeable to water but permeable to sodium • All nephrons are involved in this process • The glomerular filtration rate ensures that the elimination of compounds such as urea from plasma can take place without losing large amounts of water as well

Renal Investigations Urinalysis Significance of presence of casts in urine • Hyaline casts may be seen in normal urine, particularly after exercise • Coarse granular casts occur in glomerular and tubular disease • Tubular cell casts may be seen in patients with acute tubular necrosis • The presence of 10 or more white blood cells/mm3 infection • The presence of red-cell casts characteristic of glomerulonephritis Red cell casts: Present in: • Acute glomerulonephritis • Renal vasculitis Notes & Notes for MRCP
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• Stimulates thirst • Stimulates aldosterone and ADH • Accelerated hypertension • Interstitial nephritis.

Oliguria • Oliguria is defined as <400 ml urine/day. • a urine output of <0.5mL/kg/h. comment Normal limits urinalysis or cubic millimeter (mm3) < 10 (WBCs) / leukocytes / (pus cells) "Significant pyuria " ≥10 leucocytes per microlitre (µl) characteristic of glomerular origin 0 - 3 dysmorphic RBCs Suggestive of in vivo hemolysis but must be distinguished from hematuria. In case of hemoglobinuria, a urine dipstick shows presence of blood, but no RBCs are seen on microscopic examination.

hemoglobinuria a positive test suggests presence of bacteria in significant numbers (ie more than 10,000 per ml) , A negative result does not rule out a UTI

nitrites Sterile pyuria Definition • Pyuria in the absence of bacteriuria Causes • adult polycystic kidney disease • Chemical cystitis (eg cyclophosphamide) • analgesic nephropathy • Acute glomerulonephritis • Tubulo-interstitial diseases Glycosuria in pregnancy • The most likely mechanism of glycosuria in pregnant woman Reduced renal reabsorption • patients with persistent glycosuria should be investigated with a glucose tolerance test at around 24 weeks Ketonuria in pregnancy • Ketonuria may also be seen in normal pregnancy, as a result of the increased metabolic requirements Urine pH • The range is 4.5 to 8. urine is commonly acidic (ie 5.5-6.5) • Acidic urine (low pH) may be caused by: diet (eg, acidic fruits such as cranberries) uric acid calculi. • Urine pH generally reflects the blood pH but in renal tubular acidosis (RTA) this is not the case. In type 1 RTA (distal) the urine is acidic but the blood alkaline. Notes & Notes for MRCP
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• partially treated UTI • urethritis and sexually transmitted diseases e.g. Chlamydia • renal tuberculosis • renal stones • foreign body eg: urinary catheter, • appendicitis • bladder/renal cell cancer

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Nephrology In type 2 (proximal) the urine is initially alkaline but becomes more acidic as the disease progresses. • Alkaline urine (high pH) is seen in: the initial stages of type 2 RTA Infection with urease-splitting organisms, may be associated with the formation of stag-horn calculi. Diet, (vegetarians having more alkaline urine when compared with omnivores). Animal proteins contained in meat, eggs and cheese are often converted into acidic products (for example,

amino acids) during digestion, absorption or metabolism. This provides a daily increase in the body's acid content, which has to be excreted by the kidneys. For people eating a vegetarian diet, consumption of foods rich in citrate or carbonated drinks raise the urine pH. • Other situations can interfere with this balance, such as tubular function or bacterial infection, which often promotes an alkaline urine pH due to the presence of bacterial enzymes converting urea to ammonia. • Effects of urine pH on stone formation: Acidic urine uric acid stones are more likely to form. Alkaline urine phosphate stones are more likely to form (calcium phosphate becomes less soluble at pH>6;). • Excretion of ammonium occurs when an acid urine is produced but the pH of urine is of course determined by the concentration of H+ ions. • Unable to lower the pH to less than 5.5 in type 1 RTA. • A pH of above 7.0 after prolonged and severe vomiting would be expected in an attempt to compensate for the loss of acid; however, when there is extracellular fluid depletion the retention of sodium takes priority. Instead of bicarbonate being excreted it is reabsorbed in the proximal and distal nephron and this perpetuates the metabolic alkalosis until the fluid balance is restored with intravenous (IV) fluids. Disproportionately raised creatinine compared with the urea level leads to suspicion of rhabdomyolysis. Additional clue is raised PO4 and K+ & renal failure. Disproportionately raised urea compared with creatinine level leads to suspicion of dehydration.

Renal investigations • The most appropriate an urgent scan to exclude obstruction of the kidneys is Ultrasound renal tract • Retrograde urethro-graphy is the mainstay of investigation for urethral stricture
disease • Renal scintigraphy with DMSA Involves administration of radioactive isotope (dimercaptosuccinic acid) which is taken up by the renal parenchyma.

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 This identify regions of decreased uptake due to acute inflammation (such as pyelonephritis) or renal scarring. The technique of dimercaptosuccinic acid DMSA scan also allows detection of congenital renal disorder. A small kidney with uniform uptake of DMSA is likely to represent congenital hypodysplasia, whereas a focal area of reduced cortical uptake associated with loss of contours is more likely to represent an infection-related scar.

Renal Biopsy • The hila of the kidneys lie at the L1 and L2 vertebral levels. • For a routine biopsy there is no preferable side to biopsy, but commonly it is the Lt Kidney. • Coagulation studies should always be performed prior to renal biopsy due to the risk of bleeding (e.g. in a case of alcohol excess, clotting studies may be deranged). Complications • Macroscopic haematuria can occur in up to 10% of renal biopsies. • Nephrectomy is a rare but serious complication of renal biopsy required to control bleeding. It should be consented for that. Contraindications • Absolute contraindications to renal biopsy include the following: Uncorrectable bleeding diathesis Uncontrollable severe hypertension Active renal or perirenal infection Skin infection at biopsy site • relative contraindications to renal biopsy: Uncooperative patient Anatomic abnormalities of the kidney which may increase risk Small kidneys Solitary kidney

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Haematuria • Haematuria is defined as >3 RBC/high power field (hpf) of centrifuged sediment under the microscope. • Non-visible (Microscopic) haematuria is found in around 2.5% of the population. Causes of transient or spurious non-visible haematuria • urinary tract infection • menstruation • vigorous exercise (this normally settles after around 3 days) • sexual intercourse

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Nephrology Causes of persistent non-visible haematuria • cancer (bladder, renal, prostate) • stones • benign prostatic hyperplasia • prostatitis • urethritis e.g. Chlamydia • renal causes: IgA nephropathy, thin basement membrane disease Spurious causes - red/orange urine, where blood is not present on dipstick • foods: beetroot, rhubarb • drugs: rifampicin, doxorubicin what is the pathophysiology of Exercise-induced hematuria? Extracorpuscular mechanical trauma causing hemolysis patients present after the event with rust-colored urine. Management • Current evidence does not support screening for haematuria. • The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated. Testing • urine dipstick is the test of choice for detecting haematuria • persistent non-visible haematuria is often defined as blood being present in 2 out of 3 samples tested 2-3 weeks apart • The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated as normal. • renal function, albumin: creatinine (ACR) or protein: creatinine ratio (PCR) and blood pressure should also be checked • urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected • in an elderly presented with painless macroscopic haematuria. the most important thing to exclude after infection would be a bladder tumour initially before embarking upon a renal biopsy. Therefore cystoscopy is the best initial investigation. NICE urgent cancer referral guidelines (updated in 2015). • Urgent referral (i.e. within 2 weeks) Aged ≥45 years AND: unexplained visible haematuria without UTI, or visible haematuria that persists or recurs after successful treatment of UTI. Aged ≥60 years AND have unexplained nonvisible haematuria and either dysuria or a raised white cell count on a blood test. • Non-urgent referral Aged ≥60 years with recurrent or persistent unexplained UTI. • patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care. May 2009 exam: A 62-year-old man with H/O hypertension & AF, on warfarin. A urine dipstick showed blood + with no protein or leucocytes. This result repeated twice. What is the most appropriate action? Cystoscopy (The incidence of non-visible haematuria is similar in patients taking warfarin to the general population therefore these patients should be investigated as normal)

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Acute interstitial nephritis (AIN) Definition • Acute interstitial nephritis is inflammation of the renal tubulo-interstitium, secondary to a hypersensitivity reaction to drugs. Epidemiology • accounts for 25% of drug-induced acute renal failure Pathophysiology • The onset of AIN occurs approximately 10-14 days after the initiation of the inciting agent and resolves with removal of the offending drug. • It is typically characterized by Eosinophilia and Eosinophiluria with elevated levels of IgE in the

serum suggesting a type I hypersensitivity. • AIN may also be caused by type IV hypersensitivity with mononuclear interstitial infiltrate on renal biopsy. • Drug → Hypersensitivity reaction (type IV) within the kidney interstitium → acute kidney injury. Causes • Drugs: the most common cause NSAIDs, (The most common causative drug) Penicillin, rifampicin, cephalosporins, vancomycin, Co-trimoxazole, Sulphonamides Allopurinol Thiazides and furosemide Phenytoin Ranitidine, Cimetidine, Omeprazole • Infection: (eg, Mycoplasma) • Autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis). Features • Allergic reaction: triad of rash, fever, and eosinophilia (only in 10%) • Many patients are not oliguric despite moderately severe acute renal failure. Patients with non-oliguric acute renal failure should always be investigated for AIN • hypertension • Proteinuria is dominant Investigations • Eosinophilia is common • Urine: white cells, red cells, and white cell casts (Eosinophiluria) • Acute Kidney injury (AKI) : ↑ creatinine • Renal biopsy : for definite diagnosis → shows mononuclear cell infiltrate throughout the interstitium with associated oedema. Treatment • The majority of patients recover following withdrawal of the offending drug • High-dose prednisolone is indicated in some cases to hasten recovery. NSAID-induced AIN does not generally respond to glucocorticoid therapy. • Dialysis may be required in severe cases.

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Nephrology Prognosis • Good prognosis if it is managed early. Untreated AIN results in interstitial fibrosis. Drug induced acute interstitial nephritis (AIN) Remember these 7 P’S:

1. Pee drugs (diuretics): Thiazides and furosemide
2. Pain-free (NSAIDs)
3. Penicillins and cephalosporins
4. Proton pump inhibitors
5. Phenytoin
6. RifamPin
7. SulPha drugs: Sulfasalazine, Sulfonylureas Acute interstitial nephritis (AIN) should be suspected in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria.

Contrast induced acute kidney injury (CI- AKI) Definition • a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media. eg: iv contrast agent during angiography • A continued enhancement of the kidneys days after contrast injection suggests contrastinduced nephropathy. Features • ↑ serum creatinine within 24 to 48 hours after the iodinated contrast exposure (usually mild) Patients with oliguria and severe AKI (who may require renal replacement therapy) may be more likely to have an alternate etiology of AKI. • Most patients are nonoliguric. Oliguria may develop in patients with severe AKI and in patients with moderate to severe chronic kidney disease (CKD) at baseline. • Protein excretion is typically absent or mild (unless the patient had proteinuric CKD at baseline). • Urine: usually shows classic findings of acute tubular necrosis (ATN), including muddy brown granular and epithelial cell casts and free renal tubular epithelial cells Risk of acute kidney injury in adults having iodine-based contrast media • chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m2 are at particular risk) • diabetes but only with chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73

m2 are at particular risk) • heart failure • renal transplant • age 75 years or over • hypovolaemia • increasing volume of contrast agent • intra-arterial administration of contrast medium with first-pass renal exposure (when the contrast reaches the renal arteries in a relatively undiluted form, e.g., through injection into the left heart, thoracic and suprarenal abdominal aorta, or the renal arteries.).

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Preventing acute kidney injury in adults having iodine-based contrast media • Adequate hydration is the most important step to prevent contrast media nephropathy → (iv 0.9% sodium chloride or isotonic sodium bicarbonate) • Temporarily stop ACE inhibitors and ARBs if eGFR ˂ 40 ml/min/1.73 m2 • Metformin is usually withheld for 48 hours after the use of contrast Criteria for renal replacement therapy in AKI • if any of the following are not responding to medical management: hyperkalaemia metabolic acidosis symptoms or complications of uraemia (for example, pericarditis or encephalopathy) fluid overload pulmonary oedema. Imaging for Dialysis-dependent patients • Dialysis-dependent patients who receive contrast for a CT scan may need haemodialysis to remove the contrast. • MR contrast tends not to be nephrotoxic and therefore haemodialysis is not usually necessary to remove MR contrast. • The magnetic resonance angiography with gadolinium is not recommended because it carries a risk of nephrogenic systemic fibrosis MRCP-part-1- exam- January 2014 exam: What is the most important step in reducing the risk of contrast-induced nephropathy? Intravenous 0.9% sodium chloride pre- and post-procedure

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Nephrology

Acute tubular necrosis vs. prerenal uraemia Pre-renal uraemia Acute tubular necrosis Pathology due to hypoperfusion due to circulatory compromise and/or nephrotoxins Urine sodium < 20 mmol/L

> 30 mmol/L Urine osmolality 500 <350 Fractional sodium excretion* < 1% 1% Fractional urea excretion** < 35% 35% Urine: plasma osmolality 1.5 < 1.1 Urine: plasma urea 10:1 < 8:1 urine/plasma creatinine 40 <20 Specific gravity 1020 < 1010 Urine 'bland' sediment A urine free of red blood cells or casts brown granular casts Response to fluid challenge Yes No • *fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x

• **fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100 • 80-90% Of the acute renal failure seen by physicians will fall into the category of prerenal failure or ATN. • Normal plasma osmolality = 278 – 305 mOsmol/Kg • Normal urinary osmolality = 350 –

1000 mOsmol/Kg September 2009 exam: Which test is most useful when determining whether there is prerenal uraemia or acute tubular necrosis? Urinary sodium

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Acute tubular necrosis (ATN) Pathological mechanism • ATN usually arises following an acute ischaemic or nephrotoxic event in ischemic causes of ATN the thick ascending limb of the Loop of Henle is injured in nephrotoxic event the proximal convoluted tubule is affected. • the injured tubular cells fail to reabsorb sodium, tubular concentrating ability is lost, and urea clearance is low Causes of ATN include • Hypotension • Hypertension: Accelerated hypertension can cause small vessel obstruction with proliferative endarteritis of intralobular arteries and fibrinoid necrosis of afferent arterioles and glomerular capillary tuft. • Rhabdomyolysis • Hepatic failure: Renal failure from ATN occurs in 25% of patients with severe hepatic damage. • Eclampsia • Drugs such as : aminoglycosides, Aminoglycoside undergoes glomerular filtration and then reabsorption in the proximal tubule where tubular cell injury/death occurs. cephalosporins, cisplatin, amphotericin. Heavy metal poisoning, carbon tetrachloride, Heroin addicts. Associated furosemide is likely to increase the plasma concentration of toxic drugs and leads to (ATN). Corticosteroid therapy has not been associated with ATN. Phases: (ATN) is characterised by 3 phases:

1. Initiation phase, with acute decrease in GFR with sudden rise in serum creatinine ± oliguria
2. Maintenance phase, with a sustained marked reduction in GFR and rising Cr (1-2 weeks)
3. Recovery phase, in which tubular function is gradually restored and urine volume gradually rises, with concomitant decrease in Cr to pre-injury levels Features • Oliguria is common in the early stages of acute tubular necrosis (ATN) • ATN after aminoglycoside impairment in the concentrating ability, and most patients are non-oliguric • acute renal failure expected to begin more than five days after the initiation of gentamicin • Small amounts of 'tubular' proteinuria (<1 g/day) may be seen, but >3 g suggests a glomerular leak • Urinalysis often reveals brown granular casts, which are tubular epithelial cells. Precautions in management • After inappropriate attempts to initiate a diuresis by infusion of normal saline without adequate monitoring of the patient's volume status, pulmonary oedema due to salt and water retention is not uncommon • Aminoglycoside nephrotoxicity correlates with Frequency of aminoglycoside dosing

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Nephrology • Multiple human clinical trials (including meta-analysis) studies report less nephrotoxicity and equal efficacy when aminoglycosides are given once daily (supratherapeutic doses) rather than in conventional divided doses. Prognosis • Oliguria during the initial stages of ATN is followed by polyuria, and even after a relatively minor insult, recovery may take up to 6 weeks • Creatinine clearance would be expected to be normal in only 40% of cases one year after the initial insult. • The mortality rate associated with ATN may be up to 50%, but this is largely

dependent on the precipitating illness • the chance of recovery of renal function to the level where dialysis is not required 95 % Complication • Sepsis, particularly Gram-negative septicaemia, is the most frequent complication and cause of death in acute renal tubular necrosis while awaiting spontaneous recovery of renal function Neither the use of prophylactic antibiotics nor barrier nursing has been shown to reduce infection risk in this situation.

Papillary necrosis Causes • chronic analgesia use (concomitant diuretic use may exacerbate renal hypotension) • sickle cell disease • TB • acute pyelonephritis • diabetes mellitus UTI are relatively more common in women with diabetes. Untreated infections in people with diabetes can result in renal papillary necrosis, Features • fever, loin pain, haematuria • IVU - papillary necrosis with renal scarring - 'cup & spill' Consequences of renal papillary necrosis • Ureteric obstruction may result if the papillae have sloughed off Management • Where there is obstruction, review by a urologist is advised as ureteric stent placement may be required • If there is no obstruction withdrawal of the offending agent + adequate hydration

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Acute Pyelonephritis Epidemiology • The two peaks of incidence in adults occur in young sexually active women and in men > 50 years of age Aetiology • Gram-negative bacilli such as Escherichia coli or Klebsiella species are responsible in more than 95% of cases • Unusual organisms may be responsible if there has been a history of urethral instrumentation

• Staphylococcal urinary sepsis is usually indicative of haematological seeding of infection Symptoms • include fever, rigors, flank pain, dysuria, polyuria, haematuria, nausea and vomiting, headache and diarrhea. The absence of fever rules out acute pyelonephritis Investigations • In young women with a first infection, urine culture may be all that is required • urea and electrolytes measurement, a full blood count and blood cultures, and renal ultrasound in compromised patients Treatment • trimethoprim or ciprofloxacin • Surgical opinion may be required for: recurrent infections evidence of vesicoureteric reflux on scanning .

Acute vs. chronic renal failure Best way to differentiate is renal ultrasound - most patients with CRF have bilateral small kidneys. (normal range for both kidneys 10-12 cm) Renal size Renal size asymmetry in the presence of hypertension and renal impairment suggest renovascular disease. Small kidneys suggest chronic renal failure Causes of Large kidneys (chronic renal failure with normal/enlarged kidneys) • amyloidosis • Stage 1 diabetic nephropathy • Hydronephrosis • Rapidly progressive glomerulonephritis • HIV-associated nephropathy Causes of one small kidney • Renal arterial disease • or chronic renal scarring due to vesico-ureteric reflux (associated with recurrent UTI) Voiding cysto-urethrogram (VCUG) is the investigation of choice to demonstrate potential reflux disease Other features suggesting CRF rather than ARF • hypocalcaemia (due to lack of vitamin D) • evidence of renal osteodystrophy on plain X-ray • skin pigmentation and peripheral neuropathy are the result of long-standing metabolic abnormality such as chronic renal failure
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The usual range of kidney size measured longitudinally is between 9-12 cm. • Acromegaly • Renal vein thrombosis • Adult polycystic kidney disease • Scleroderma

Nephrology

Cholesterol embolization Overview • cholesterol emboli may break off causing renal disease • seen more commonly in arteriopaths, abdominal aortic aneurysms Features • eosinophilia • purpura • renal failure • livedo reticularis MRCPUK-part-1-May 2014 exam: H /O impaired RFT + purpuric rash on feet after coronary angiogram is performed for acute MI. What is the most likely diagnosis? Cholesterol embolization (Cholesterol embolisation is a well-documented complication of coronary angiography)

Chronic kidney disease (CKD) Definition • Impaired renal function for >3 months based on abnormal structure or function, (GFR ˂ 60 mL/minute/1.73 m²) Common causes • diabetic nephropathy (Type II > type I) • hypertension • chronic glomerulonephritis (commonly IgA nephropathy) • chronic pyelonephritis • adult polycystic kidney disease Investigations • Creatinine-based estimate of glomerular filtration rate (eGFR) If eGFR result is less than 60 ml/min/1.73 m2 in a person not previously tested, what is the next step → Repeat the test within 2 weeks. The most commonly used formula now is the CKD-EPI equation (more accurate than the old MDRD equation), which uses the 4 variables: serum creatinine, age, gender and ethnicity. The new 2021 version of CKD-EPI equation does not include a term for race. Factors, which may affect the result muscle mass ↓muscle mass (e.g. amputees, body-builders) → overestimation.↑ muscle mass →underestimation. eating red meat 12 hours prior to the sample being taken pregnancy • Urine albumin to creatinine ratio (ACR): the first initial test for Albuminuria ACR ˃ 30 mg/g indicates albuminuria If ACR 30 - 70 mg/mmol → repeat with early morning sample to confirm If ACR ≥70 mg/mmol →no need to repeat • Urine for haematuria Diagnosed by reagent strips , no need to use urine microscopy to confirm • Renal doppler ultrasound the first-line imaging technique for the assessment of kidney structure. Helps to diagnose CKD if kidney atrophy is present

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Creatinine-based estimate of GFR VS Cystatin C-based estimate of GFR • There are no difference in the bias between the equations, • Precision may be worse with cystatin C-based estimates. • Creatinine-based estimate of GFR are recommended by NICE as initial first choice • When to use a cystatin C-based estimate of GFR for diagnosis of CKD? (Nice 2014) If creatinine based eGFR is 45–59 ml/min/1.73 m2, sustained for at least 90 days + no proteinuria or other marker of CKD →do eGFR cystatin C, if it is more than 60 ml/min/1.73 m2 → rule out CKD Creatinine-based estimate of glomerular filtration rate (eGFR) • 2 formulas are used Modification of Diet in Renal Disease (MDRD) equation Uses the 4 variables: serum creatinine, age, gender and ethnicity. Paradoxical higher risk observed in people at higher eGFR Performs better at lower levels of GFR CKD-EPI equation more accurate than MDRD equation Less bias at eGFR > 60 , similar performance at eGFR ˂ 60. Recommended now as the best equation The new version (2021) of this equation does not include a term for race Classification of CKD Stage Description eGFR

(ml/min) Notes

Normal

> 90 with other evidence of chronic kidney damage e.g. Albuminuria

Mild impairment 60-89 with other evidence of chronic kidney damage 3a Moderate impairment 45-59 with or without evidence of chronic kidney damage 3b Moderate impairment 30-44 with or without evidence of chronic kidney damage

Severe impairment 15-29 with or without evidence of chronic kidney damage

End stage renal failure (ESRF) Less than 15 or on dialysis Features • Early stages are often asymptomatic • Symptoms usually only occur once stage 4 is reached (GFR <30). • Symptoms of end-stage renal disease (eg, pruritus, refractory electrolyte imbalances, metabolic acidosis, severe nausea, neurologic impairments) typically occur when GFR is 5 to 10 mL/minute/1.73 m²

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Nephrology

Consequences of CKD • Hyperkalaemia CKD → metabolic acidosis → causes the ion to exit the intracellular space to the extracellular → ↑↑serum potassium CKD → decreased potassium excretion • Hyperphosphataemia : CKD → ↓ phosphate excretion→ ↑ hyperphosphatemia. • Secondary Hyperparathyroidism: ↓ Ca2+ + ↑ serum phosphate → ↑PTH • Metabolic acidosis is a result of bicarbonate wasting and reduced ammonia and acid excretion. • Hypertension: due to sodium and water overload and direct renal effects secondary to the underlying renal disease. • Anaemia due to decreased erythropoietin production, low grade haemolysis, inadequate intake ↓ synthesis of erythropoietin → ↓ stimulation of RBC production → normocytic, normochromic anemia • Hypertriglyceridaemia Due to decreased plasma lipoprotein lipase activity • Pericarditis and cardiomyopathy uraemia leads to exudation of fibrin onto the epicardial and pericardial surfaces. • Glucose intolerance: due to tissue insulin resistance. • Cardiovascular-associated CKD-complications • Increased risk of vascular diseases: Increased risk of coronary artery disease and stroke A falling GFR is an independent risk factor for cardiovascular disease this is the chief cause of death from renal failure. • Increased skin pigmentation Chronic kidney disease (CKD): Disorders of mineral and bone metabolism Hypocalcaemia • Secondary to reduced levels of 1,25(OH)2 vitamin D ↓ Renal hydroxylation of vitamin D → ↓ 1,25-(OH)2 vitamin D3 → ↓ intestinal Ca2+ absorption → ↓ Ca2+ • Secondary to hyperphosphataemia ↓ Renal excretion of phosphate → hyperphosphatemia → calcium-phosphate precipitation in tissues → ↓ Ca2+ Hyperphosphataemia PO(4) ↑↑: Due to reduced phosphate excretion. Secondary hyperparathyroidism • hyperphosphataemia and hypocalcaemia → ↑↑parathyroid hormone (secondary hyperparathyroidism) → renal osteodystrophy.

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Renal osteodystrophy • Definition: Renal osteodystrophy refers to specific changes in bone morphology associated with CKD. The term "renal osteodystrophy" is exclusively used to define bone pathology observed on biopsy. • Diagnosis PTH is the best noninvasive test for the assessment of bone turnover. Bone biopsy is the gold standard for diagnosing renal osteodystrophy and identifying the specific type. • Subtypes include osteitis fibrosa cystica, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy (MUO). Osteitis fibrosa cystica characterized by high bone turnover due to persistently high PTH. There is a marked increase in the number and activity of osteoblasts (ie, bone-forming cells) and osteoclasts (bone-reabsorbing cells) and an increase in osteoid (unmineralized bone). PTH >450 pg/mL suggests osteitis fibrosa cystica Adynamic bone disease most common form of renal osteodystrophy observed in dialysis patients, particularly diabetic patients. characterized by low bone turnover with reductions in both osteoblast and osteoclast activity. Risk factors include the use of calcium-containing phosphate binders, highdialysate calcium, and the use of active vitamin D analogs. Features: usually asymptomatic, bone pain. Complications: fractures, hypercalcemia, and vascular calcification Suggested diagnosis among dialysis patients →very↓↓(PTH; ie, <100 pg/mL) especially if hypercalcemia is present. Suggested diagnosis among patients who are not on dialysis →Initially high PTH and progressively ↓↓ less than normal during treatment with vitamin D analogs. normal or low bone-specific alkaline phosphatase (BSAP) Treatment: by allowing PTH secretion to rise. using non-calcium-containing phosphate binders rather than calciumcontaining phosphate binders decrease the dose or stop calcitriol and all active vitamin D analogs For dialysis patients →use low-calcium dialysate (ie, 2 mEq/L) rather than standard (ie, 2.5 mEq/L) Osteomalacia characterized by decreased mineralization, causing an increase in unmineralized osteoid caused by aluminum deposition in bone. uncommon in ESKD patients since aluminum-based phosphate binders were abandoned Extra-skeletal calcification (Metastatic calcification) • mainly due to calcium phosphate deposition, • Increased prevalence with time on haemodialysis • CKD managed with dialysis is the commonest cause of secondary oxalosis (acute arthritis of small joints with digital calcific deposits). • Calciphylaxis: a rare complication of end-stage renal failure. Pathophysiology: deposition of calcium within arterioles causing microvascular occlusion and necrosis of the supplied tissue.

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Nephrology Features: most commonly affects the skin and presents with painful necrotic skin lesions. Risk factors: hypercalcaemia, hyperphophataemia and hyperparathyroidism. Exacerbating factors: Warfarin is widely reported as causing/exacerbating calciphylaxis in high risk patients, however the underlying mechanism is not known. Treatment: reducing calcium and phosphate levels and controlling hyperparathyroidism avoiding contributing drugs such as warfarin and calcium containing compounds. Management • Reduce hyperphosphataemia Phosphate binders 1st line: calcium based binders such as calcium acetate is the most appropriate initial treatment. the additional calcium in calcium acetate may be sufficient to increase the plasma calcium into the normal range. Side effects : vascular calcification 2nd line: if calcium acetate is not indicated (eg, hypercalcaemia or low serum parathyroid hormone levels)

or not tolerated → Offer sevelamer carbonate aluminium containing binders are no longer used Dialysis Dialysis is able to remove only about half of the phosphate that the healthy kidney would be able to do. The healthy adult kidney excretes 5400 mg per week of phosphate. the maximum amount of phosphate that can be removed by dialysis in a patient with anuric renal failure who is dialysis dependent is 2700 mg / week. • Reduce PTH level → vitamin D chronic renal failure and hypocalcaemia with a raised parathyroid hormone (PTH) secondary hyperparathyroidism. Chronic renal failure leads to hyperphosphataemia, which triggers release of parathyroid hormone. Studies such as UKPDS reveal that: • improving glycaemic control would reduce microvascular complications but this has no significant impact upon cardiovascular morbidity and mortality. • lowering blood pressure significantly reduced morbidity from both microvascular and macrovascular disease.

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eGFR variables => CAGE => Creatinine, Age, Gender, Ethnicity MRCPUK-part-1-January 2010 exam: Which factor is most likely to invalidate the use of the Modification of Diet in Renal Disease (MDRD) equation to calculate a patients eGFR? Pregnancy MRCPUK-part-1-May 2012 exam: Which factor is most likely to explain unexpectedly low result of eGFR? Large muscle mass secondary to body building

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Diabetic nephropathy Definition • Persistent albuminuria due to glomerular injury that is caused by prolonged exposure to hyperglycemia Epidemiology • Diabetic nephropathy is a major cause of end stage renal disease (ESRD). • The peak incidence of frank albuminuria is 17 years after diagnosis of type 1 diabetes Pathophysiology • Seen in patients with diabetes for > 10 years • Glomerulosclerosis the most common renal complication of DM • The characteristic microscopic changes which will confirm a diagnosis of diabetic nephropathy Focal nodular mesangial tissue expansion Kimmelstiel-Wilson lesion → Pathognomonic nodular glomerulosclerosis Risk factors Modifiable Non-modifiable • Hypertension • Hyperlipidaemia • Smoking • Poor glycaemic control • Raised dietary protein • Male sex • Duration of diabetes • Genetic predisposition (e.g. ACE gene polymorphisms)

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Nephrology Stages Stage Description Stage 1 • hyperfiltration: increase in GFR • may be reversible Stage 2 (silent or latent phase) • most patients do not develop microalbuminuria for 10 years • GFR remains elevated Stage 3 (incipient nephropathy) • microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative) Stage 4 (overt nephropathy) • persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive) • hypertension is present in most patients • histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules) Stage 5 • end-stage renal disease, GFR typically < 10ml/min • renal replacement therapy needed Diagnosis • Microalbuminuria is the earliest clinical sign of diabetic nephropathy. • Urinary albumin to creatinine ratio ≥30 mg/g, GFR ˂ 60 mL/minute/1.73 m^2 Absence of albuminuria in patients with diabetes and a reduced estimated GFR raises the possibility of nondiabetic chronic kidney

disease Management • Optimal glycaemic and blood pressure control BP control: aim for < 130/80 mmHg Early antihypertensive treatment delays the progression of diabetic nephropathy. ACE inhibitors or angiotensin receptor blockers, are the preferred drugs The best therapeutic option to prevent progression of renal disease Treat with ACEI (superior to glycaemic control)

CKD: anaemia Causes of anaemia in renal failure • reduced erythropoietin levels - the most significant factor Investigations: diagnostic tests • Hypochromic red blood cells content (% HRC; ˃ 6%) • If using % HRC is not possible, use reticulocyte Hb content (CHr; ˂ 29 pg) • If % HRC & CHr are not available, use Combination of transferrin saturation (˂ 20%) and serum ferritin measurement (˂100 micrograms/litre). Management • 1st step: correct iron status with oral or iv Most non haemodialysis patient may take oral iron . In contrast most haemodialysis patients will require intravenous iron Transfusions in patients awaiting renal transplants are usually avoided where possible, due to the potential risk of circulating antibodies and thus organ rejection.

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 If the patient is haemodynamically unstable and an urgent blood transfusion is advised (e.g. symptoms and signs of severe anaemia, i.e. angina): → postpone transplant for at least 3 months, following repeat antibody screening. • 2nd step: Once iron stores are restored and ferritin is in the normal range, if the patient is still anaemic then erythropoietin would be the next appropriate option • Targets for treatment Hb: 10 - 12 g/dl (NICE 2015) Ferritin: 200-500 µg/L (NICE 2015 advice: ferritin should not rise ˃ 800 mic/litre & review iron dose when ferritin reach 500. Transferrin saturation >20% haematocrit <33%. percentage hypochromic red cells <6%. Current Renal Association guidelines suggest that the target Hb for patients receiving erythropoetin therapy is between 105-125 g/L.

CKD - Management Referral criteria for specialist assessment • Risk of needing renal replacement therapy • ACR ≥70 mg/mmol (unless diabetic) • ACR ˃30 mg/mmol + haematuria • ↓↓ eGFR ≥25% and a change in eGFR category within 12 months • ↓↓ eGFR ≥15 ml/min/1.73 m2 per year • Poorly controlled hypertension despite the use of at least 4 antihypertensive medicines • Suspected renal artery stenosis or genetic causes of CKD Chronic Kidney Disease CKD: management of hypertension • Hypertension is both a cause and consequence of chronic kidney disease. • Treatment Angiotensin-receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor: the 1st line for CKD + ACR > 30. Side effects: NICE suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable. A rise greater than this may indicate underlying renovascular disease. Furosemide is useful as anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*.(*the NKF K/DOQI guidelines suggest a lower cutoff of less than 30 ml/min) • Target range for BP in CKD: NICE guidelines recommend that: CKD + proteinuria ACR ˂70 mg/mmol →˂ 140/90 (target range 120-139/<90). CKD + proteinuria ACR ≥70 mg/mmol or DM →˂ 130/80 (target range 120129/<80). Chronic Kidney Disease : Diagnosis and management of proteinuria • Diagnosis: Proteinuria (ACR ≥3 mg/mmol) Urine reagent strips are not used Urine Albumin: creatinine ratio (ACR) is the first initial test

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 If ACR 3 - 70 mg/mmol → repeat with early morning sample to confirm If ACR ≥70 mg/mmol → no need to repeat Microalbuminuria is defined as a urine albumin excretion of between 30-300 mg per 24 hours. in non-diabetics an ACR greater than 30 mg/mmol is considered clinically significant proteinuria in diabetics microalbuminuria (ACR greater than 2.5 mg/mmol in men and ACR greater than 3.5 mg/mmol in women) is considered clinically significant. • Management CKD + DM + ACR ≥ 3 mg/mmol → ARB or an ACE inhibitor CKD without diabetes + ACR ≥ 70 mg/mmol → ARB or an ACE inhibitor & nephrologist assessment CKD without diabetes + ACR above 30 but below 70 mg/mmol → monitor Spironolactone The second choice to reduce proteinuria after ACEi Side effects: hyperkalaemia & small ↓in GFR Effects of ARB or ACE inhibitor on CKD • ↓↓ proteinuria & BP • ↓↓ breakdown of bradykinin (an efferent arteriolar vasodilator); • ↓↓ production of cytokines, such as transforming growth factor–beta (TGF-beta), that promote glomerulosclerosis and fibrosis. ARB or ACE inhibitor in CKD (NICE guidelines/ November 2021) • Monitor serum potassium before starting and 1 and 2 weeks after starting or increasing the dose. If potassium ˃ 5.0 mmol/litre : do not start If potassium ≥ 6.0 mmol/litre: stop ARB or an ACE inhibitor • Monitor eGFR before starting and 1 and 2 weeks after starting or increasing the dose. If eGFR ↓↓ by ˂ 25% or serum creatinine ↑↑ by ˂ 30% of baseline: do not modify the dose and repeat the test in 1 to 2 weeks. If eGFR ↓↓ by ≥ 25%, or serum creatinine ↑↑ by ≥30%: look for other causes (e.g., NSAIDs), stop or reduce the dose and add an alternative antihypertensive if needed.

Prescribing in patients with renal failure Questions regarding which drugs to avoid in renal failure are common Drugs to avoid in renal failure • antibiotics: tetracycline, nitrofurantoin • NSAIDs NSAIDs reduce glomerular perfusion by inhibiting production of prostaglandins which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function. Thus, the most likely cause of renal decline is prostaglandin related. NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture.

• lithium • metformin Drugs likely to accumulate in chronic kidney disease - need dose adjustment • most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin • digoxin, atenolol • methotrexate • sulphonylureas • furosemide • opioids Alfentanil, buprenorphine and fentanyl are the preferred opioids in patients with chronic kidney disease. Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease • antibiotics: erythromycin, rifampicin • diazepam • warfarin • Omeprazole is principally dependent upon hepatic clearance and safe even with marked renal impairment. •

Erythropoietin • Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes. Sources of Erythropoietin • interstitial fibroblasts in the kidney (predominant during adulthood) • perisinusoidal cells in the liver (predominates in the fetal period) • Exogenous erythropoietin, or recombinant human erythropoietin (rhEPO), is produced by recombinant DNA

technology . The main uses of erythropoietin are • to treat the anaemia associated with chronic kidney disease The best option to relieve fatigue in patient with end stage renal failure is Treatment of anaemia with erythropoietin Improvement in haemoglobin level results in the increased well-being and better appetite. • Anaemia associated with cytotoxic therapy. • Prevention of anaemia in premature babies with low birth weight. Side effects of erythropoietin • accelerated hypertension headache, encephalopathy & seizures (BP ↑↑in 25%) • ischaemic stroke • bone aches • flu-like symptoms • skin rashes, urticaria • pure red cell aplasia (PRCA)

• raised PCV thrombocythaemia ↑ risk of thrombosis (e.g. Fistula) • iron deficiency 2nd to increased erythropoiesis • anaphylaxis • Hyperkalaemia in uraemic patients • ↑mortality of patients with malignancy (e.g. renal cell carcinoma)

Chapter 6

Nephrology

Causes of response failure to erythropoietin therapy: • iron deficiency • inadequate dose • concurrent infection/inflammation • hyperparathyroid bone disease • aluminium toxicity : if suspected, perform a desferrioxamine test • folate deficiency ESA induced pure red cell aplasia (PRCA) • due to antibodies against erythropoietin • Indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. • Confirmed by presence of anti-erythropoietin antibodies together with a lack of pro erythroid progenitor cells in the bone marrow • the risk is greatly reduced with darbepoetin Treatment protocol • Ideally, before starting EPO in renal patients you should get their haematinics (iron, B12, folate) to ensure they are replete of all. If any are found to be low they should be replaced. • Parameters commonly measured to assess iron status are: serum ferritin and transferrin saturation. Both are indirect measures of iron and frequently do not permit an assessment of the adequacy of iron supply to the erythron. direct measures by flow cytometry, cell volume and hemoglobin concentration can be measured in individual red blood cells and reticulocytes, using two parameters (particularly useful in identifying iron-deficient erythropoiesis). The percentage of hypochromic erythrocytes (defined as red blood cells with a hemoglobin concentration of less than 28 g/dl) the content of hemoglobin in reticulocytes (CHr) • If there is Iron deficiency (NICE 2015) For patient on haemodialysis or ESA I.V iron therapy. For patient not on haemodialysis trial of oral iron If they are intolerant of oral iron or target Hb levels are not reached within 3 months intravenous iron therapy. (part 2 Exam July 2002) offer maintenance iron to people with anaemia of CKD who are receiving ESAs haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (1 mg/kg/week). [NICE 2015] • If Ferritin is below the recommended level of 200 for patients receiving erythropoietin treatment iron supplementation is recommended. GI absorption of iron is suboptimal in patients with renal failure, and IV replacement is therefore the preferred intervention. • Erythropoietin is given subcutaneously at a dose of 25-50 U/kg three times per week • The blood pressure, haemoglobin and reticulocyte count should be monitored every 2 weeks • erythropoiesis-stimulating agent (ESAs): dose and frequency adjusted to keep the rate of Hb increase between 10 and 20 g/litre/month. • Adjusting ESA treatment if ACEi & ARB are used, an increase in ESA therapy should be considered. ferritin should be >200g/l in patients treated with

EPO. Notes & Notes for MRCP
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• marrow fibrosis • development of antibodies against the treatment • ESA-induced PRCA • testosterone deficiency in males • poor compliance

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Significance of erythropoietin levels (EPO test) • Low serum erythropoietin levels suggest polycythaemia vera • raised serum erythropoietin level suggests hypoxic cause autonomous production of erythropoietin (as in renal carcinoma). erythropoietin abuse (Erythropoietin has been misused as a performanceenhancing drug by some athletes) May 2010 exam: H/O CKD patient started on erythropoietin. What is the main benefit of this treatment? Improved exercise tolerance Erythropoietin can be detected in urine for few weeks after the latest dose Renal replacement therapy • Patients usually begin dialysis when their glomerular filtration rate (GFR) reaches 10 ml/minute or 15 mL/minute if they are diabetic. Indications for dialysis • Refractory pulmonary oedema • Persistent hyperkalaemia (K+ >7mmol/L) • Severe metabolic acidosis (pH<7.2 or base excess <10) • Uraemic complications such as encephalopathy or Uraemic pericarditis (pericardial rub) Uraemic peripheral neuropathy • Drug overdose—BLAST: Barbituates, Lithium, Alcohol (and ethylene glycol), Salicylates, Theophyline, Vascular access for routine haemodialysis • Arterio-venous fistula: Current Renal Association guidelines state that an arterio-venous fistula is the first choice of vascular access for dialysis. arterio-venous fistulas are preferred due to their longevity and lower risk of infection. Arterio-venous grafts: using prosthetic material, have a reduced longevity compared to arterio-venous fistulas. These are second choice preference for vascular access. Dialysis catheters (tunnelled and non-tunnelled): carry a risk of infection and are not preferred as first line. They can be used when emergency dialysis is required, or as an interim measure when awaiting more permanent dialysis access. Arterio-venous fistula is the first choice of vascular access for dialysis.