

Third edition

# Notes & Notes

For MRCP part 1 & 11

By

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# Nephrology

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## Chapter 6 Nephrology

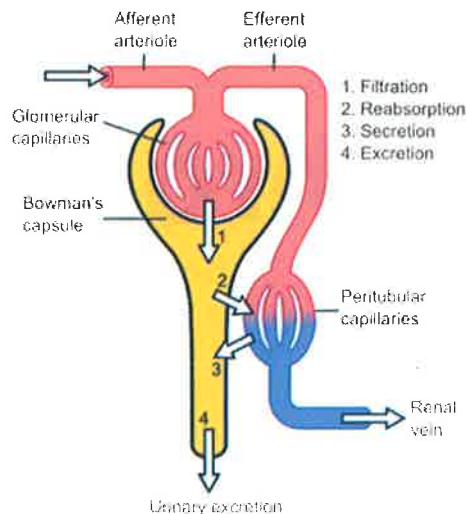
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**Renal anatomy** The tables below show the anatomical relations of the kidneys:**Right kidney**

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

**Left kidney**

Direct contact	Layer of peritoneum in-between
Left suprarenal gland <b>Pancreas</b> Colon	Stomach Spleen Distal part of small intestine

**Renal physiology**

Excretion = Filtration – Reabsorption + Secretion

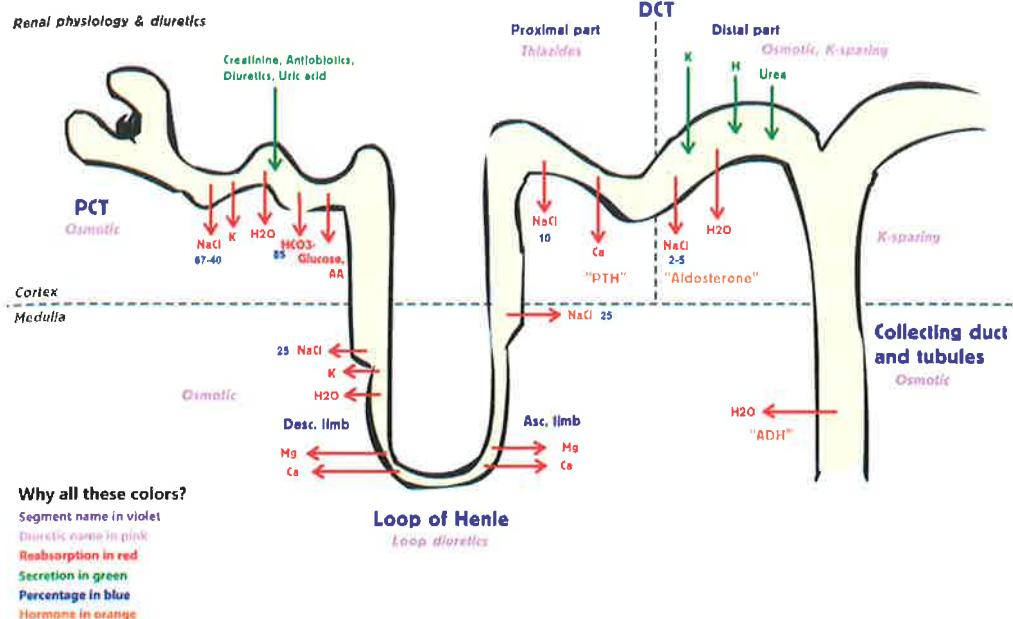
Diagram showing the basic physiologic mechanisms of the kidney

**Renal blood flow (RBF)**

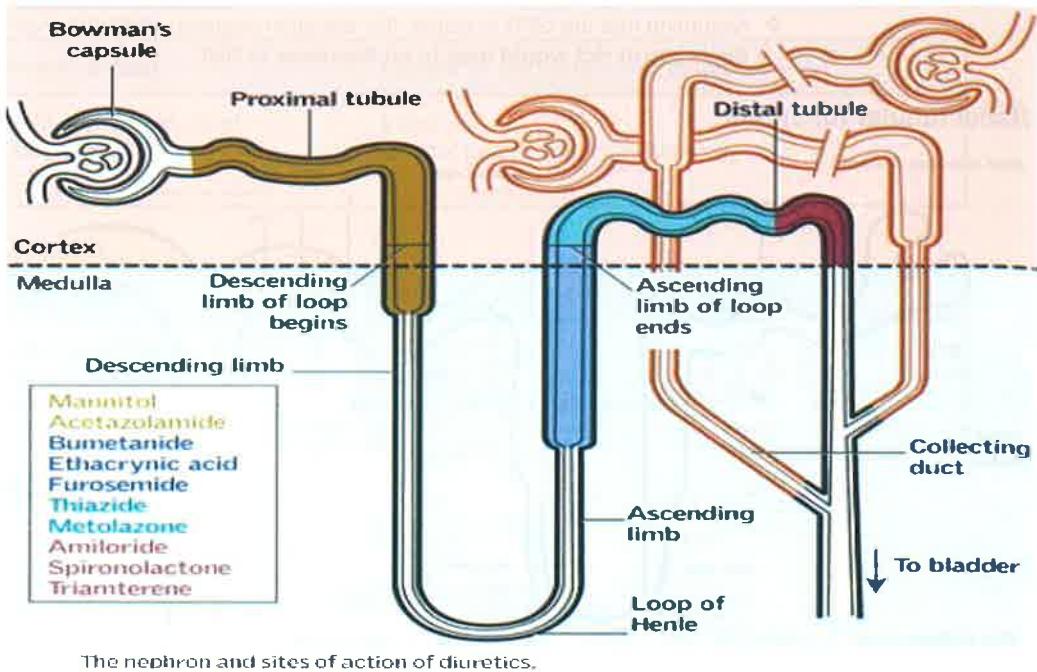
- **Renal blood flow is 20-25% of cardiac output**
- **The 'Fick principle' can be used to estimate RBF through clearance.**
- Sympathetic stimuli produce vasoconstriction and RBF should be increased in response to hypoxia.
- Renal cortical blood flow > medullary blood flow (i.e. tubular cells more prone to ischaemia)
- **Glomerular filtration rate and renal blood flow increase by about 50% in pregnancy** leading to **decreased BUN and creatinine** on laboratory examination.
- **What is the effect of decrease in hematocrit on renal function?**
  - **Decreased Renal Blood Flow**
  - the relationships between Renal Blood Flow (RBF), Renal Plasma Flow (RPF), Hematocrit (Hct), and Glomerular Filtration Rate (GFR):

- ❖ RBF = RPF / (1 - Hct).
- ❖ Assuming that the GFR is stable, this equation suggests that a **decrease in Hct would lead to a decrease in RBF.**

## Renal tubular functions



- Sodium, glucose, bicarbonate and amino acids are absorbed at the proximal tubule level
- Sodium reabsorption is mostly through active transport in the loop of Henle with only a modest reabsorption facilitated by aldosterone.
- Ammonia is secreted by the distal tubule
- Regulation of water secretion is by the distal tubule and the collecting ducts under the influence of vasopressin → increase permeability to water.
- The relative hyperosmolality of the medulla is maintained by a counter-current mechanism and is responsible for the flux of water across the renal tubule
- descending loop of Henle is permeable to water but impermeable to solutes, due to the presence of aquaporin 1 in its tubular wall → water moves to medullary space → hypertonic filtrate
- ascending loop of Henle is impermeable to water (because of a lack of aquaporin, a common transporter protein for water channels in all cells except the walls of the ascending loop of Henle) but permeable to solutes, but here Na<sup>+</sup>, Cl<sup>-</sup>, and K<sup>+</sup> are actively transported into the medullary space, making the filtrate hypotonic
- What is the renal cellular mechanism that prevents a sodium load intake from drastically increasing plasma osmolality?
  - Movement of aquaporin channels to the apical surface of collecting duct cells
  - An increase in sodium intake will cause an increase in plasma osmolality, triggering the release of antidiuretic hormone (ADH), a.k.a. vasopressin.
    - ❖ The immediate effect of ADH (occurs over minutes) → movement of aquaporin channels to the apical surface of collecting duct cells.
    - ❖ the long-term effect of ADH (occurs over days) → Increase in aquaporin gene expression by collecting duct cells.

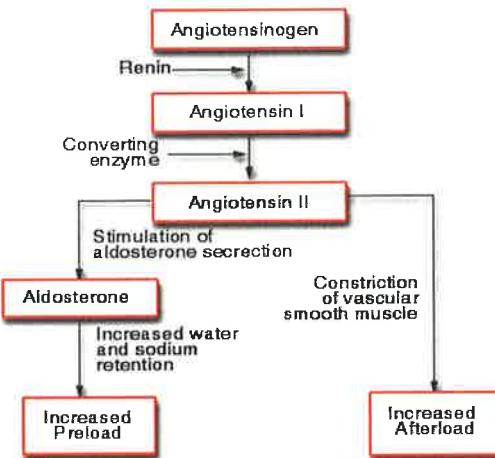


### Renal Physiology of Pregnancy

- Kidneys size increase by 1 to 1.5 cm during pregnancy.
- Kidney volume increases by up to 30%, primarily due to an increase in renal vascular and interstitial volume.
- Glomerular filtration rate (GFR) and renal blood flow rise markedly during pregnancy, resulting in a physiologic fall in the serum creatinine concentration. A serum creatinine of 1.0 mg/dL in a pregnant woman probably reflects significant renal insufficiency.
  - The glomerular filtration rate **increases** 50% with subsequent **decrease** in serum creatinine, urea, and uric acid values.
- **mechanisms** contribute to decreased vascular resistance, increased renal plasma flow, and increased GFR during pregnancy:
  - **Reduced vascular responsiveness to vasoconstrictors** such as angiotensin 2, norepinephrine, and antidiuretic hormone.
  - Additionally, the ovarian hormone and vasodilator relaxin is a key mediator of **enhanced nitric oxide signaling in pregnancy**.
- **The best method to estimate GFR in pregnancy is by 24-hour urine collection for creatinine clearance.**
  - Completeness of the collection should be confirmed by checking the 24-hour creatinine excretion (10 to 15 mg creatinine/day per kg body weight is consistent with a complete collection).
  - Estimating equations, such as the Modification of Diet in Renal Disease Study (**MDRD**) and Chronic Kidney Disease Epidemiology Collaboration (**CKD-EPI**) equations, are **not accurate in pregnancy**.
  - Physiologic ureteral dilatation (hydronephrosis and hydroureter) is common during pregnancy, and results from:

- 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

**Angiotensin**

- ACE in lung converts angiotensin I → angiotensin II
- Vasoconstriction leads to raised BP
- Stimulates thirst
- Stimulates aldosterone and ADH

**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<sup>+</sup> in exchange for K<sup>+</sup>/H<sup>+</sup> :
  - ↑ resorption of Na<sup>+</sup> → ↓Na<sup>+</sup> loss in urine
  - ↑ resorption of water (osmotic effect due to ↑ Na<sup>+</sup>)
  - ↑ excretion of K<sup>+</sup>

**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/mm<sup>3</sup>** → infection
- **The presence of red-cell casts** → characteristic of glomerulonephritis

**Red cell casts**: Present in:

- Acute glomerulonephritis
- Renal vasculitis
- Accelerated hypertension
- Interstitial nephritis.

## Oliguria

- Oliguria is defined as <400 ml urine/day.
- a urine output of <0.5mL/kg/h.

urinalysis	Normal limits	comment
(WBCs) / leukocytes / (pus cells)	< 10	"Significant pyuria" $\geq$ 10 leucocytes per microlitre ( $\mu\text{l}$ ) or cubic millimeter ( $\text{mm}^3$ )
dysmorphic RBCs	0 - 3	characteristic of glomerular origin
hemoglobinuria	0	Suggestive of <i>in vivo</i> 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.
nitrites	0	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

## 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
- 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

## Glycosuria in pregnancy

- **The most likely mechanism of glycosuria in pregnant woman**  $\rightarrow$  **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.

- 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<sup>+</sup> 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 PO<sub>4</sub> and K<sup>+</sup> & 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.

- 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

## **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**

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• urinary tract infection</li> <li>• menstruation</li> </ul> | <ul style="list-style-type: none"> <li>• vigorous exercise (this normally settles after around 3 days)</li> <li>• sexual intercourse</li> </ul> |
|---|---|

**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?**

→ **Extracorporeal 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  $\geq 45$  years AND:
    - unexplained visible haematuria without UTI, or
    - visible haematuria that persists or recurs after successful treatment of UTI.
  - Aged  $\geq 60$  years AND have unexplained nonvisible haematuria and either dysuria or a raised white cell count on a blood test.
- **Non-urgent referral**
  - Aged  $\geq 60$  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)

## 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.

## 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 contrast-induced 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 m<sup>2</sup> are at particular risk)
- diabetes but only with chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m<sup>2</sup> 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.).

## 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 m<sup>2</sup>
- 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**

## Acute tubular necrosis vs. prerenal uraemia

ATN or prerenal uraemia? In prerenal uraemia think of the kidneys holding on to sodium to preserve volume

	Pre-reenal 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 <b>A urine free of red blood cells or casts</b>	brown granular casts
Response to fluid challenge	Yes	No

- \*fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100
- \*\*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**

## 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**

- 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

## 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**

**The usual range of kidney size measured longitudinally is between 9-12 cm.**

**Causes of Large kidneys → (chronic renal failure with normal/enlarged kidneys)**

- amyloidosis
- Stage 1 diabetic nephropathy
- Hydronephrosis
- Rapidly progressive glomerulonephritis
- HIV-associated nephropathy
- Acromegaly
- Renal vein thrombosis
- Adult polycystic kidney disease
- Scleroderma

**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

## Cholesterol embolization

### Overview

- cholesterol emboli may break off causing renal disease
- seen more commonly in arteriopathies, abdominal aortic aneurysms

### Features

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• eosinophilia</li> <li>• purpura</li> </ul> | <ul style="list-style-type: none"> <li>• renal failure</li> <li>• livedo reticularis</li> </ul> |
|---|---|

**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 m<sup>2</sup>)

### 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 m<sup>2</sup> 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

### 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 m<sup>2</sup>, 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 m<sup>2</sup> → 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
1	Normal	>90	with other evidence of chronic kidney damage e.g. Albuminuria
2	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
4	Severe impairment	15-29	with or without evidence of chronic kidney damage
5	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 m<sup>2</sup>

## 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**: ↓ Ca<sup>2+</sup> + ↑ 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 anaemia
- **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)<sub>2</sub> vitamin D**
  - ⇒ ↓ Renal hydroxylation of vitamin D → ↓ 1,25-(OH)2 vitamin D3 → ↓ intestinal Ca<sup>2+</sup> absorptio i → ↓ Ca<sup>2+</sup>
- **Secondary to hyperphosphataemia**
  - ⇒ ↓ Renal excretion of phosphate → hyperphosphatemia → calcium-phosphate precipitation in tissues → ↓ Ca<sup>2+</sup>

**Hyperphosphataemia PO(4) ↑↑:** Due to reduced phosphate excretion.

### Secondary hyperparathyroidism

- hyperphosphataemia and hypocalcaemia → ↑↑ parathyroid hormone (secondary hyperparathyroidism) → renal osteodystrophy.

## 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, high-dialysate 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 calcium-containing 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.

- ⇒ **Features:** most commonly affects the skin and presents with painful necrotic skin lesions.
- ⇒ **Risk factors:** hypercalcaemia, hyperphosphataemia 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**

- **1<sup>st</sup> 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
- **2<sup>nd</sup> 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.

CKD: only diagnose stages 1 & 2 if supporting evidence to accompany eGFR

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

## 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
<ul style="list-style-type: none"> <li>Hypertension</li> <li>Hyperlipidaemia</li> <li>Smoking</li> <li>Poor glycaemic control</li> <li>Raised dietary protein</li> </ul>	<ul style="list-style-type: none"> <li>Male sex</li> <li><b>Duration of diabetes</b></li> <li>Genetic predisposition (e.g. ACE gene polymorphisms)</li> </ul>

**Stages**

Stage	Description
Stage 1	<ul style="list-style-type: none"> <li>hyperfiltration: increase in GFR</li> <li>may be reversible</li> </ul>
Stage 2 (silent or latent phase)	<ul style="list-style-type: none"> <li>most patients do not develop microalbuminuria for 10 years</li> <li>GFR remains elevated</li> </ul>
Stage 3 (incipient nephropathy)	<ul style="list-style-type: none"> <li>microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative)</li> </ul>
Stage 4 (overt nephropathy)	<ul style="list-style-type: none"> <li>persistent proteinuria (albumin excretion &gt; 300 mg/day, dipstick positive)</li> <li>hypertension is present in most patients</li> <li>histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)</li> </ul>
Stage 5	<ul style="list-style-type: none"> <li>end-stage renal disease, GFR typically &lt; 10ml/min</li> <li>renal replacement therapy needed</li> </ul>

**Diagnosis**

- Microalbuminuria is the earliest clinical sign of diabetic nephropathy.
- Urinary albumin to creatinine ratio  $\geq 30 \text{ mg/g}$ , GFR  $< 60 \text{ mL/minute}/1.73 \text{ m}^2$ 
  - 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  $< 130/80 \text{ mmHg}$**
  - 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;  $< 29 \text{ pg}$ )
- If % HRC & CHr are not available, use Combination of **transferrin saturation** ( $< 20\%$ ) and **serum ferritin** measurement ( $< 100 \text{ micrograms/litre}$ ).

**Management**

- 1<sup>st</sup> 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.

- 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.
- 2<sup>nd</sup> 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 erythropoietin 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 m<sup>2</sup> 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 1<sup>st</sup> 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 cut-off 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 **120-129/<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

- If ACR 3 - 70 mg/mmol → repeat with early morning sample to confirm
- If ACR  $\geq$  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  $\geq$  3 mg/mmol → ARB or an ACE inhibitor
  - ⇒ CKD without diabetes + ACR  $\geq$  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  $\geq$  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  $\geq$  25%, or serum creatinine ↑↑ by  $\geq$  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

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• accelerated hypertension → headache, encephalopathy &amp; seizures (BP ↑↑ in 25%)</li> <li>• ischaemic stroke</li> <li>• bone aches</li> <li>• flu-like symptoms</li> <li>• skin rashes, urticaria</li> <li>• pure red cell aplasia (PRCA)</li> </ul> | <ul style="list-style-type: none"> <li>• raised PCV thrombocythaemia → ↑ risk of thrombosis (e.g. Fistula)</li> <li>• iron deficiency 2nd to increased erythropoiesis</li> <li>• anaphylaxis</li> <li>• Hyperkalaemia in uraemic patients</li> <li>• <b>↑mortality of patients with malignancy (e.g. renal cell carcinoma)</b></li> </ul> |
|--|---|

**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
- marrow fibrosis
- development of antibodies against the treatment
- **ESA-induced PRCA**
- testosterone deficiency in males
- poor compliance

**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.**

## 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 performance-enhancing 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

CKD on haemodialysis - most likely cause of death is IHD

- 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 ( $K^+ > 7 \text{ mmol/L}$ )
- Severe metabolic acidosis ( $\text{pH} < 7.2$  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, Theophylline,

### 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 (tunneled and non-tunneled):
  - 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.**

## Haemodialysis (HD)

### Assessment of haemodialysis adequacy:

The adequacy of haemodialysis session is best measured by :

- 'Clearance' is used to indicate dialysis adequacy, and most commonly the clearance of urea is used.
  - Clearance is the ratio of removal rate to blood concentration.
  - Removal rate can be measured by sampling blood on either side of the dialyser and multiplying the difference by the inflow rate.
  - Clearance is the removal rate divided by the inflow concentration.
  - However, this only provides a measure of **dialysis at one point in time**.
- The adequacy of an **entire haemodialysis session** is best measured by the fall in solute concentration from before dialysis to after.
  - This is calculated using complex equations and is expressed as Kt/V.
  - The current recommendation for adequate dialysis for three treatments per week are a Kt/V of 1.2.
- (the 'urea reduction ratio'). A more crude assessment of the adequacy of dialysis obtained by noting the magnitude of the decrease in blood urea concentration
- It is standard practice in the UK to take biochemical and haematological measurements before and after haemodialysis sessions at regular intervals (monthly in hospital HD patients and at least 3 monthly in home HD patients). Adequate HD is indicated by:
  - pre-dialysis serum bicarbonate levels of 18-24 mmol/L,
  - potassium 4.0-6.0 mmol/L,
  - phosphate 1.1-1.7 mmol/L,
  - calcium and albumin within normal range.

### Pre and post- dialysis values:

- A high pre-dialysis or inter-dialysis blood pressure may be related to:
  - excessive sodium and water ingestion during the inter-dialysis period
  - or a high dialysate sodium level,
- A high post-dialysis blood pressure may reflect inadequate achievement of dry weight.
  - Volume and blood pressure are linked and it is therefore important to optimise ultrafiltration and dry weight to control blood pressure.
  - A patient's dry weight is their normal weight when they are not fluid overloaded, also called euvoolemia
  - The rate of **ultrafiltration** depends upon the porosity of the membrane and the hydrostatic pressure of the blood, which depends upon blood flow. This is very effective in removal of fluid and middle-sized molecules, which are thought to cause uremia.
- Weight gain between dialyses of more than 4.8% is associated with increased mortality.
- **The combination of high pre- and post-dialysis blood pressure, and high pre-dialysis potassium, indicate that the patient is receiving inadequate dialysis.**
  - Both procedural issues (insufficient blood flow rate, **dialysis time and frequency** and needle size) and access issues should be addressed.

- If these fail to improve the situation a different dialysis modality should be considered, such as more frequent or sustained haemodialysis.
- It is recommended that pre-dialysis haemoglobin concentration should be maintained between 100-120 g/L.
  - If his haemoglobin below the recommended level for a dialysis patient, you need to measure haematinics initially prior rather than jumping in with EPO treatment.
  - Many haemodialysis patients are iron deplete, and in these cases intravenous iron is indicated rather than EPO in the first instance.

### Adverse effects of dialysis

- Modern techniques of dialysis preclude chances of vitamin D or calcium deficiency, fluid and electrolyte imbalance or risk of viral hepatitis
- **protein-calorie malnutrition is the most common problem associated with haemodialysis**
  - **seen in up to 50% of patients**
  - Dietary restriction of foods with high phosphate content (milk, eggs and cheese), decreased protein intake, anorexia, nausea and vomiting, may all contribute to this condition

### Complications of rapid haemodialysis

- **Disequilibrium syndrome:**
  - Caused by cerebral oedema, resulting from the rapid shifts of uraemic toxins associated with too-rapid haemodialysis in a severely uraemic patient
  - characterized by weakness, dizziness, headache, and in severe cases, mental status changes.
  - The diagnosis is one of exclusion;
  - a prime characteristic of this syndrome is that it is nonfocal.

### Long-term haemodialysis

- **associated with carpal tunnel syndrome this is due to beta-2 microglobulin deposition**
- **Cardio-vascular disease is the commonest cause of death (50%) in dialysis patients**
- **Carnitine deficiency**
  - Patients on chronic hemodialysis may have carnitine deficiency.
  - Carnitine is essential for the transport of long-chain fatty acids from the cytosol into the mitochondria.
  - **chronic hemodialysis → carnitine deficiency → Impaired mitochondrial transport of long-chain fatty acids**
  - Cardiomyocytes and skeletal muscle cells extensively use fatty acids as a fuel.
  - Carnitine deficiency leads to:
    - accumulation of long-chain fatty acids in the cytosol of cardiomyocytes (resulting in cardiac fatty change and **cardiomegaly**)
    - accumulation of long-chain fatty acids in the cytosol of skeletal muscle cells (resulting in **muscle cramps**).
  - **Treatment** is via L-carnitine administration.

## Line-related infection

A patient with a tunneled haemodialysis catheter who develops a fever on dialysis should be considered to have line-related infection until proven otherwise.

- The most common organisms for line-related sepsis are gram-positive bacteria, namely *S. aureus*.
- Blood cultures should be taken from the line and peripherally, and if the same organism is growing from them both, this strongly suggests the line is the source of the infection.
- **Indications of Catheter removal :**
  - *Staphylococcus aureus* bloodstream infection
  - non-staphylococcus aureus catheter-related bloodstream infection in the following circumstances:
    - Severe sepsis
    - Haemodynamic instability
    - Endocarditis
    - Evidence of metastatic infection, or
    - Persistence of bacteraemia after 48-72 hours of effective antibiotics.
- **Treatment**
  - *Methicillin-resistant Staphylococcus aureus (MRSA) infection*
    - vancomycin is the drug of choice

## Dialysis amyloidosis

### Aetio-pathogenesis

- Occurs due to the failure of clearance of **B2-microglobulin**
  - This protein, the light chain of class-1 HLA antigens, is usually freely filtered at the glomerulus but is not cleared by cellulose-based dialysis membranes
- There is resulting amyloid deposition within the synovium

**Clinical features:** Amyloid deposition within the synovium results in:

- **clinical syndrome of median nerve compression**
- **pain and stiffness in multiple joints**

### Treatment & Prognosis

- The syndrome resolves slowly after renal transplantation,
- some benefit is seen in switching patients to dialysis with a biosynthetic dialysis membrane

### Complications:

- gastrointestinal haemorrhage caused by amyloid deposition around submucosal blood vessels

## Peritoneal dialysis

- Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.
- The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day.

### Complications:

- Peritoneal dialysis-associated peritonitis
- sclerosing peritonitis
- Adynamic bone disease (ABD)

## Peritoneal dialysis-associated peritonitis

- Causes:
  - The most common cause → coagulase-negative staphylococci such as *Staphylococcus epidermidis* (40-50% of cases).
  - another common cause → *Staphylococcus aureus*
- Diagnosis
  - is made by peritoneal fluid cell count (**neutrophils above 100/ml.**) ( White cell count  $> 100/\text{mm}^3$  in PD fluid sample )
  - PD fluid neutrophil percentage of greater than 50% is in keeping with PD peritonitis.
- Treatment
  - **intraperitoneal antibiotics** (vancomycin) And oral quinolone (Before culture results are received).
    - the initial treatment of choice would be intraperitoneal antibiotics.
    - initial antibiotic regimes should cover Gram positive (including MRSA) and Gram-negative organisms.
      - ❖ Give intra-peritoneal vancomycin and gentamicin
  - Intravenous antibiotics would be preferable if the clinical condition **worsened despite intraperitoneal antibiotics**,
  - Recurrent Staph, epidermidis peritonitis may necessitate **removal and replacement of the peritoneal dialysis catheter** due to chronic colonisation

## Adynamic bone disease (ABD) → (low bone turnover)

- Definition: (ABD) is a variety of renal osteodystrophy characterized by reduced osteoblasts and osteoclasts, no accumulation of osteoid and markedly low bone turnover ( $\downarrow$ bone formation and resorption).
- Distinguish ABD from the second low-turnover form, i.e. osteomalacia:
  - In ABD: Both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen are subnormal. there are few or no osteoblasts
  - In osteomalacia: mineralization defect exceeds the defects in bone formation, resulting in a relative osteoid excess.
  - Bone alkaline phosphatase (BAP) is the single most useful biochemical parameter for the assessment of bone formation.
    - $\uparrow$  BAP exclude ABD
    - elevations of BAP along with total AP may be seen in severe osteomalacia.
- Risk factors & Causes: overtreatment of secondary hyperparathyroidism associated with CKD (ABD is, at least in part, often iatrogenic)
  - commonly CKD patients on dialysis, either peritoneal or hemodialysis
    - $\uparrow$  in CAPD compared to haemodialysis
    - Especially prevalent in diabetic patients on peritoneal dialysis
    - $\uparrow$  in age of dialysis patients
  - Aluminum overload
    - Serum aluminium levels do not correctly reflect body aluminium stores and do not correlate well with signs of aluminium toxicity.
    - desferrioxamine (DFO) test increases the diagnostic accuracy
  - High calcium load
  - Low PTH levels
  - Vitamin D over-treatment (eg : alfacalcidol)
  - High prevalence of diabetes mellitus
- Pathophysiology:
  - basically in CKD:
    - PTH serum levels are higher than normal

- bone tissue is resistant to PTH
- PTH serum levels decrease beyond relatively low levels, which would be considered normal in the general population.
- So that a relative reduction of PTH → low turnover state.
- **Complications:** (pain, fracture,↑ Ca+)
  - bone pain
  - increased incidence of hip fracture
  - hypercalcaemia as the bone loses its capacity to buffer serum calcium
- **Treatment:** currently follows two principles:
  1. reduce calcium and vitamin D load
    - Stop calcium-containing phosphate binders and replace with non-calcium-, non-aluminium-containing phosphate binders
    - Assess oral dietary calcium intake and reduce to <2000 mg/day
    - Reduce or stop active vitamin D compounds
    - Lower dialysate calcium to 1.25 mmol/L or below
    - Avoid bisphosphonates, strontium and fluoride administration
  2. restore PTH activity
- **Follow-up**
  - Changes of bone markers, such as bone-specific alkaline phosphatase, over time, may be suitable indicators for the assessment of therapeutic effects.

### Other complications of peritoneal dialysis

- **Worsening of diabetic control:**
  - dialysis fluid contains a high glucose
  - **patients with diabetes may require significantly more diabetes treatment to reduce their blood glucose once dialysis is commenced**
- **Worsening of abdominal hernias:** due to the large fluid volume expansion and should be surgically repaired
- **Stomas adhesions:**
  - **Stomas may be associated with significant adhesions and changes within the abdominal cavity making catheter placement impossible**

### Contraindication of continuous ambulatory peritoneal dialysis (CAPD):

- Colostomy.
  - increase the risk of peritonitis
- Recent or prospective abdominal surgery
  - **Complex abdominal surgery** and resultant extensive adhesion damage the peritoneal membrane (peritoneal fibrosis) and lead to compartments within the peritoneum.
  - Simple abdominal surgery, however, does not preclude peritoneal dialysis; examples include cholecystectomy, appendectomy or caesarian section.

**May 2013 exam:** A patient on Ambulatory Peritoneal Dialysis (CAPD). Feels generally unwell with abdominal pain and fever. Which organism is most likely to be responsible for this presentation?

→ ***Staphylococcus epidermidis***

## Renal transplant

Cytomegalovirus is the most common and important viral infection in solid organ transplant recipients

Hyperacute graft rejection is due to pre-existent antibodies to HLA antigens and is therefore IgG mediated

Renal transplant HLA matching → DR is the most important

### Some basic points on the HLA system

- class 1 antigens include A, B and C. Class 2 antigens include DP, DQ and DR
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A
- **Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?**
  - HLA-C
    - Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection;
    - specifically, HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant.

### Types of Transplants:

- **Autografts:**
  - same individual acts as both donor and recipient.
- **Isografts:**
  - donor and recipient are genetically identical (twins).
- **Allografts:**
  - donor and recipient are genetically dissimilar but belong to the same species (the commonest).
- **Xenografts:**
  - donor and recipient belong to different species (between animal and human).
- **Orthotopic transplants:**
  - the transplanted part is placed in its normal anatomical location.
- **Heterotopic transplants:**
  - the transplanted part is placed in different anatomical location.

Graft survival	1 year	10 years
Cadaveric transplants	90%	60%
Living-donor transplants	95%	70%

### Post-operative problems

- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

### Hyper acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction) and is therefore IgG mediated
- rarely seen due to HLA matching
- antigen-antibody complexes → activate the complement system → causing massive thrombosis in the capillaries → avascularization of the graft.

- the kidney is most susceptible to hyperacute rejection; the liver is relatively resistant, possibly because of its dual blood supply, but more likely because of incompletely understood immunologic properties.

**Reasons for deterioration in renal function soon after a renal transplant:**

- Hyperacute rejection (which usually occurs in hours)
- Acute tubular necrosis, and
- Surgical complications (renal arterial or venous thrombosis and ureteric stenosis).

In the presence of a dropping urine output and rising creatinine, an urgent ultrasound scan should be obtained to exclude any mechanical obstruction of the renal tract before considering other options.

**Acute graft failure (< 6 months)**

- Approximately 25% of transplant patients will have at least one episode of rejection mostly between days 7 and 21, and less commonly up to three months post-operation.
- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
  - Although CMV infection would not cause a sudden deterioration in renal function
- Doppler ultrasound studies may show a sharp deterioration in graft perfusion, and kidney biopsy will show invading lymphocytes penetrating the tubular basement membrane, causing tubulitis.
- It is often clinically silent, with only a sharp rise in serum creatinine pointing towards the diagnosis.
- may be reversible with steroids and immunosuppressants

**Chronic graft failure (> 6 months)**

- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- caused by recurrence of original renal disease (MCGN > IgA > FSGS)
  - Recurrence of renal pathologies post-renal transplantation:
    - Membranoproliferative GN: 40-90% recurrence rate, type 2 much greater than type 1).
    - FSGS: 40%.
    - Membranous GN: 30%.

**Differentiate between acute cellular rejection and CMV**

	Onset	Feature	Renal function
<b>Acute cellular rejection</b>	Commonly between days 7 and 21	often clinically silent	Sudden sharp rise in serum creatinine
<b>CMV</b>	Usually seen after four weeks	Systemic feature (pulmonary, GIT and Retinitis).	Gradual rise in serum creatinine

**Risk factors of chronic rejection include:**

- number of previous acute rejection episodes
- presence of anti-HLA antibodies**
- anti-endothelial antibodies
- CMV infection
- dyslipidaemia
- hypertension
- functional mass of the donor kidney, and
- delayed graft function (a clinical manifestation of ischaemia/reperfusion injury).

Type of transplant rejection	Hyperacute rejection	Acute rejection	Chronic rejection
<b>Frequency</b>	• < 1%	• 50%	• 50%
<b>Onset after transplantation</b>	• <b>&lt; 48</b> (usually within minutes to hours)	• <b>&lt; 6 months</b> (usually within days to weeks)	• <b>&gt; 6 months</b> (usually after a few years)
<b>Pathophysiology</b>	• <b>Preformed antibodies against class I HLA</b> → activation of complement system and adhesion to granulocytes → thrombosis of vessels → graft ischemia	• T-lymphocyte induced cell-mediated and/or humoral immunity	• Irreversible intimal fibrosis and obstruction of vessels
<b>Clinical findings</b>	• <b>Intraoperative assessment:</b> swelling of the organ as soon as perfusion is restored	• Pain in the graft region • Graft edema • Fever and deterioration of general condition • In kidney transplants: ↑ BP and RFT; ↓ urine output	• Slow, progressive loss of organ function
<b>Diagnosis</b>	• Biopsy: small vessel thrombosis and graft infarction	• Biopsy (confirmatory test) ➤ Heterogenous mononuclear aggregates± antibody deposition ➤ <b>C4d</b> staining indicates <b>humoral</b> graft rejection ➤ Negative <b>C4d</b> staining indicates <b>cellular</b> rejection	• Biopsy ➤ Kidney: Glomerular sclerosis ➤ Heart: accelerated coronary artery disease ➤ Liver: vanishing bile duct syndrome
<b>Prevention</b>	• Preoperative cross-matching, ABO grouping and HLA matching	• Post-transplant immunosuppressive therapy	• Irreversible process with no known prevention
<b>Treatment</b>	• Graft removal	• Change or <b>increase dosage of immunosuppressive therapy</b>	• Graft removal, and re-transplantation

## Graft versus host disease (GVHD)

**presents with liver abnormalities, significant diarrhoea and skin changes.**

### Definition

- damage to the host as a result of a systemic inflammatory reaction induced by T lymphocytes present in the graft

### Etiology

- Allogeneous hematopoietic stem-cell transplantation
- Small bowel transplantation
- Transfusion of non-irradiated blood products

➤ **Products implicated in cases of transfusion associated GVHD include:**

- Non-irradiated whole blood
- **Packed red blood cells**
- Platelets
- Fresh **non-frozen** plasma
- Granulocytes

➤ **The following have not been implicated:**

- Frozen deglycerolised red blood cells
- FFP and
- Cryoprecipitate

### Types of graft-versus-host disease

	Acute graft-versus-host disease	Chronic graft-versus-host disease
<b>Onset</b>	<ul style="list-style-type: none"> <li>• &lt; 100 days after transplantation</li> </ul>	<ul style="list-style-type: none"> <li>• &gt; 100 days after transplantation</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• Donor T lymphocytes react with the recipient's organs</li> </ul>	<ul style="list-style-type: none"> <li>• Mostly unknown</li> </ul>
<b>Clinical presentation</b>	<ul style="list-style-type: none"> <li>• Pruritic or painful maculopapular rash</li> <li>• Nausea, vomiting, <b>diarrhea</b>, and/or cramping abdominal pain</li> <li>• Hepatic dysfunction: jaundice</li> </ul>	<ul style="list-style-type: none"> <li>• Scleroderma-like and lichenoid skin changes</li> <li>• Sicca syndrome: xerophthalmia, xerostomia, dry pruritic skin</li> <li>• Chronic enteritis (similar to inflammatory bowel disease): bloody diarrhea, abdominal pain, weight loss</li> <li>• Hepatic dysfunction: jaundice</li> <li>• <b>Bronchiolitis obliterans:</b> chronic cough, wheezing, and dyspnea that is not responsive to bronchodilator therapy</li> <li>• Myasthenic symptoms</li> <li>• polymyositis: weakness, muscle pain</li> </ul>
<b>Diagnostics</b>	<ul style="list-style-type: none"> <li>• CBC: anemia, thrombocytopenia, leukopenia</li> <li>• ↑ ALP</li> <li>• Confirmatory test: biopsy of skin, rectum, or liver</li> </ul>	<ul style="list-style-type: none"> <li>• Spirometry: obstructive lung disease</li> <li>• Confirmatory test: biopsy of the skin, oral cavity, liver, or lung</li> </ul>
<b>Prevention</b>	<ul style="list-style-type: none"> <li>• <b>Antithymocyte globulin</b></li> <li>• <b>Cyclosporine</b> and one of the following:           <ul style="list-style-type: none"> <li>➢ Methotrexate</li> <li>➢ Mycophenolate mofetil</li> </ul> </li> </ul>	
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Optimize GvHD prophylaxis (e.g., cyclosporine levels)</li> <li>• Corticosteroids           <ul style="list-style-type: none"> <li>➢ &lt; 50% skin involvement: <b>topical steroids</b></li> <li>➢ Involvement of the GI tract, liver, or &gt; 50% of skin: <b>systemic steroids</b> ± topical steroids</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• First-line: <b>corticosteroids</b></li> <li>• Second-line : cyclosporine and increased corticosteroid dose</li> </ul>

## Post-transplant problems

### Cytomegalovirus (CMV) infection

Renal transplant + infection → CMV

- **Epidemiology**
  - Over 50% of renal transplant patients have a significant infection within the first 12 months of having a renal transplant.
- **Risk factors**
  - Two main factors determine whether a patient will develop CMV infection after transplantation :
    - Whether the donor or recipient harbours a latent virus capable of reactivation after transplantation
      - ❖ At the time of transplant, the CMV-serological status of the donor and recipient are noted.
      - ❖ the highest risk is seen in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor.
        - ➡ These patients are usually given antiviral prophylaxis.
      - ❖ Primary disease is the commonest and most severe type of post-transplant CMV infection.
        - ➡ This occurs in individuals who have never been infected with CMV who receive an allograft that contains latent virus from a CMV-seropositive donor.
    - The degree of immunosuppression after transplantation.
      - ❖ CMV infection occur as a result of immunosuppression
      - ❖ **Usually seen after four weeks as before this time the immune system has not been fully affected by the immunosuppressants.**
- **Features**
  - ⇒ Interstitial pneumonitis
  - ⇒ Oesophagitis
  - ⇒ Peptic ulceration
  - ⇒ Colitis and
  - ⇒ Retinitis.
- **Complications**
  - graft rejection
  - renal artery stenosis.
- **Management**
  - ⇒ **Ganciclovir (synthetic guanine derivative) is the most appropriate treatment for CMV**
    - concomitant use with ciclosporin leads to elevated creatinine
    - Pancytopenia may occur as a result of ganciclovir toxicity
  - ⇒ **Foscarnet** is the drug of choice for **ganciclovir-resistant cytomegalovirus retinitis.**

**the two most common causes of declining renal function post renal transplant are:**

- **graft rejection and**
- **ciclosporin toxicity.**

**Acute pyelonephritis:**

- **high risk of acute episode of pyelonephritis in the transplanted kidney, due to the immunosuppression, the neuropathic bladder and self-catheterisation.**

- present like an acute rejection episode, with a tender swollen graft, low-grade pyrexia, and deteriorating graft function.
- Especially in the intermediate stage of the post-transplantation immunosuppression, when the patient is most immunocompromised (three to six months post-transplant).

### **Interstitial pneumonia**

- **Cytomegalovirus is the predominant cause of infection in patients within a period of 1-4 months after renal transplantation**
- A chest X-ray will show a bilateral interstitial or reticulonodular infiltrate that begins in the periphery of the lower lobes and spreads centrally and peripherally

### **BK virus:**

- C4d staining is used for detection of BK virus after renal transplantation

### **Epstein-Barr virus (EBV)**

- **Epstein-Barr virus (EBV)-associated lymphoproliferative disease** (e.g: non-Hodgkin's lymphoma) may occur in individuals with inherited or acquired immunodeficiency syndromes.
- **Approximately 1% of renal transplant recipients develop post-transplant lymphoproliferative disease (PTLD) in the first year following their transplant.**

### **skin cancer**

- Kidney transplant recipients have a high risk of developing **non-melanoma skin cancer**, therefore, cancer surveillance is an important consideration in kidney transplant recipients
- The patient may have a **malignant melanoma with liver metastases**, hence the deranged liver function tests and liver capsule pain.
- The patient is often unaware of the melanoma lesion, and the primary lesion may in fact disappear as the disease progresses. Patient may present with RUQ pain and high LFT.
- Post-transplant patients are much more prone to develop malignancy compared to normal population.
  - ⇒ **Cyclosporine is one of the main reasons for development of post-transplant malignancy.**
- Non-melanoma skin cancers (NMSC) are the commonest malignancies in post-transplant state. Of these, **squamous cell Ca is the commonest**.

### **Kidney donation**

- Providing there is a sibling who is proven not to have polycystic kidney disease, living related donation should be considered as this would ensure a better match and better graft survival.
- Siblings are close genetically, and therefore usually are a better match than spouses. **The husband should not be accepted for kidney donation until all siblings have been considered**
- The age difference is not, however, a contraindication to kidney donation.
- Living unrelated kidney donation could also be considered, and is increasing in use in the UK.
- Adults should be considered as donor prior to children because renal cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20.

## Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD type 1 = chromosome 16 = 85% of cases

ADPKD type 2 = chromosome 4 = 15% of cases

Ultrasound is the screening test for adult polycystic kidney disease

### Epidemiology

- ADPKD is the most common inherited cause of kidney disease,
- affecting 1 in 1,000 Caucasians.
- Accounting for approximately 8% of cases of end-stage renal disease (ESRD).
- Typically presents between the ages of 30-50.

### Genetics

- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively
- **As it is an autosomal dominant, the chance of passing this condition from affected patient to his son is 50%.**

### Types

ADPKD type 1	ADPKD type 2
85% of cases	15% of cases
Chromosome 16	Chromosome 4
Presents with renal failure earlier, reach ESRF by 50s.	Have a slower course, reaching ESRF by 70s.

### Features

- Hypertension (the **earliest** manifestation of ADPKD)
- recurrent UTIs
- abdominal pain ('**loin pain due to a cyst haemorrhage** or infection)
- renal stones
- haematuria (**rupture cysts** presents with **visible haematuria**) (Gross haematuria in ADPKD carries a poor prognosis however microscopic haematuria may be a complication)
- chronic kidney disease

### Renal Complications

- CKD
  - ⇒ ADPKD is like a CKD with high phosphate, low calcium but with normal/high Hb due to excess erythropoietin secretion.
- Excessive erythropoietin production → polycythaemia.
- Renal cell carcinoma with lung metastasis: it is very rare but recognized complication of ADPKD → CT Thorax & Abdomen.

### Extra-renal manifestations

- Liver cysts (70%)
- Berry aneurysms (8%)

- ⇒ Subarachnoid haemorrhage may be a cause of mortality in 9% of patients with ADPKD,
- ⇒ 8% of patients have an asymptomatic intracranial aneurysm
- ⇒ **screening for cerebral aneurysms should only be carried out in high risk patients.** These include factors such as:
  1. Previous rupture of aneurysm
  2. Concerning neurological symptoms (for example, severe headache)
  3. Positive family history of haemorrhagic stroke or aneurysm.
- ⇒ Even if aneurysms are found, the rupture risk can still be low, and the morbidity implications of curative surgery may outweigh conservative management.
- **Cardiovascular system: mitral valve prolapse (25%)** → (needs echo screening), mitral/tricuspid incompetence, aortic root dilation, aortic dissection
- Colonic diverticula (with any related symptoms, screen by barium enema)
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary

### Investigations

- **Ultrasound** (Sensitivity for ADPKD1 is 99% for at-risk patients **older than 20 years**)
  - ⇒ **Sonographic diagnostic criteria** (in patients with positive family history):
    - age < 30 years → 2 unilateral or bilateral cysts
    - age 30-59 years → 2 cysts in each kidney
    - age > 60 years → 4 cysts in each kidney
  - ⇒ **Sensitivity of these criteria**
    - nearly 100% for patients 30 years of age or older and for younger patients with PKD1 mutations,
    - 67% for patients with PKD2 mutations younger than 30 years of age.
    - CT scan or MRI should therefore be used in the latter group.
    - one cannot be confident a child has not been affected **until they are at least 20:**
      - ❖ **a normal ultrasound scan at 20 years of age means you can be 90% confident they are not affected,**
      - ❖ a normal scan at 30 increases the confidence level to 98%.
  - ⇒ Screening is not usually recommended in children because the presence or absence of cysts does not affect management (tight blood pressure control), and the absence of cysts in children does not exclude the disease.
  - ⇒ All children of affected patients should have their blood pressure monitored at least annually, from early childhood (around age 3) onwards.
  - ⇒ If cysts are not seen in a younger with a positive family history, the ultrasound should be repeated every five years until the age of 30.
- **Contrast-enhanced CT scan or MRI**
  - ⇒ Abdominal CT is sensitive for the detection of cysts however the high radiation dose, particularly in young patients, means it is not widely used as a screening test.
  - ⇒ should be used if ultrasound is equivocal, especially in patients with PKD2 mutations younger than 30 years of age.
  - ⇒ **CT:** More sensitive than USS and may aid in diagnosis in younger patients.
  - ⇒ **MR angiography:** In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms.
- **Genetic testing**
  - ⇒ **The most appropriate strategy to investigate younger with a family history of ADPKD is genetic counselling (referral)**

- ⇒ The major indication for genetic screening in (ADPKD) is for subjects who are considering donating a kidney to a relative affected by the disease
- ⇒ **sequence analysis** can identify only around 70% of known mutations and **linkage analysis** requires the availability of sufficient family members.
- ⇒ can be used in the following cases:
  - The imaging results are equivocal or inconclusive.
  - To confirm a presumed diagnosis in the absence of family history of the disease (conclusive proof of the diagnosis in these patients relies on mutation analysis).
  - When a definite diagnosis is required in a younger patient, such as a potential living related kidney donor.
- **Renal biopsy is contraindicated** due to a high risk of haemorrhage into a cyst

### Treatment

- high fluid intake (to prevent the formation of renal stones or blood clots)
- non-NSAID-based analgesia are the cornerstones of management
  - ⇒ **IV fluids, paracetamol and codeine**
- Hypertension → ACE inhibitors or angiotensin receptor antagonists
  - ⇒ ACE inhibitors reduce proteinuria and may reduce cyst formation in ADPKD,
  - ⇒ aliskiren, the direct renin inhibitor, also has early data which show promise with respect to reducing new cysts.
- A new therapy (**tolvaptan**) to delay disease progression (recommended by NICE in 2015)
  - ⇒ **Action:** selective vasopressin antagonist → inhibit the binding of vasopressin to the V2 receptors → reduces cell proliferation, cyst formation and fluid excretion.
  - ⇒ **adverse reactions:** thirst, polyuria, nocturia, pollakiuria (frequent urination), ↑ liver enzyme.
- Urinary tract infections should be treated with lipophilic drugs (for example, ciprofloxacin, trimethoprim-sulphamethoxazole) as they have the best penetration into cyst fluid.
- The patient should be offered **genetic counselling**, despite the fact that the disease has a variable clinical course even between affected family members.
- End-stage renal disease → Transplantation

### Prognosis

- the renal function usually deteriorates in a gradual fashion, **usually with a drop in creatinine clearance of 5/6 ml/min/year**
- **Approximately half of patients require dialysis by the age of 60**

**MRCPUK-part-1-January 2016 exam: You are reviewing a patient with adult polycystic kidney disease. Which cardiovascular feature are you most likely to find on examination?**

→ **Mitral valve prolapse**

## **Autosomal recessive polycystic kidney disease (ARPKD)**

- Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD).
- **It is due to a defect in a gene located on chromosome 6**
- Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios.
- **End-stage renal failure develops in childhood.**
- Patients also typically have liver involvement, for example portal and interlobular fibrosis.
- Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

## **Medullary sponge kidney**

- is a disorder characterised by dilatation of the collecting ducts in the papillae, with accompanying cystic changes
- It is often associated with **calculi**, which can result in pyelonephritis and renal tract obstruction.
- **Typically, not inherited but is a congenital condition.** The aetiology is uncertain, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age.
- The kidneys size are normal or increased.
- The age of presentation is usually in the third or fourth decade
- The majority of cases are sporadic, although a rare autosomal dominant familial form exists with onset in adulthood, and a juvenile autosomal recessive form is also recognised. Recent research has identified a possible defect in the development of the proton pump mechanism in the kidney.
- **Diagnosis**
  - Diagnosis is made via **excretion urography**, showing small calculi in the papillary zones with surrounding increase density; this is because the dilated collecting ducts are filled with contrast medium
  - About 20% of patients have associated **hypercalciuria** or **renal tubular acidosis**
  - Skeletal hemihypertrophy may be associated
  - Renal failure is highly unusual

## **Alport's syndrome**

Alport's syndrome - X-linked dominant (in the majority)

Alport's syndrome - type IV collagen defect

- Alport syndrome is the second most common inherited cause of renal failure (after polycystic kidney disease)
- usually inherited in an **X-linked dominant** pattern.
  - Inheritance is variable, but the majority are X linked dominant (85%) ;
    - Therefore, as only the Y chromosome is passed from father to son there is no chance of the son having the disease.

- 15% are autosomal recessive with rare autosomal dominant variants
- Most cases arise from the COL4A5 gene on the X chromosome .
- It is due to a defect in **the gene which codes for type IV collagen** resulting in an **abnormal glomerular-base ment membrane (GBM)**.
  - Patients with Alport syndrome are **at risk of** developing antiglomerular basement membrane disease (**Goodpasture's disease**) **following transplantation**, as their immune systems have never been exposed to type IV collagen and hence lack tolerance.
  - **What is the most likely reason for the decline in graft function?**
    - **Anti-glomerular-base ment membrane antibodies (Goodpasture's syndrome )**
- There is a high spontaneous mutation rate, which means 20% of patients have no family history.
- Prevalence is around **1 in 5000**
- The disease is more severe in males with females rarely developing renal failure
- usually presents in childhood.
- more severe in males
  - females do not develop progressive renal failure with this condition.
- **A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture**

#### Features

**"Can't see, can't pee, can't hear a bee."**

- microscopic haematuria
  - Most common and earliest manifestation
- progressive **renal failure**
- bilateral **sensorineural deafness** (usually occurs before the onset of renal failure)
- ocular
  - **Anterior lenticonus**
    - protrusion of the lens surface into the anterior chamber
    - Occurs in 25% of patients
    - is the **pathognomonic** feature of Alport syndrome
  - Dot-and-fleck retinopathy
    - **Most common ocular manifestation** of patients with Alport syndrome, (occurring in 85%)
  - retinitis pigmentosa

#### Investigations

- renal biopsy:
  - **Light microscopy**
    - **usually unremarkable and electron microscopy is usually required.**
  - **Electron microscopy**
    - **splitting of lamina densa**
      - ❖ basket weave pattern of glomerular basement membrane
    - **foam cells**
      - ❖ produced by lipid accumulation in visceral epithelial cells
- slit lamp examination:
  - bilateral thin lens capsules
  - conical protrusions on the anterior aspect of the lens,
  - **subcapsular cataracts.**

### Treatment

- Rigorous control of hypertension may delay the onset of end stage renal failure,
- angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers if they have proteinuria
- Renal transplant

### Prognosis

- ESRF seen in 90% of patients with Alport's by the age of 40 years.

**MRCPUK-part-1-September 2009 exam:** What is the mode of inheritance of Alport's syndrome in the majority of cases?

→ X-linked dominant

**MRCPUK-part-1-January 2008 exam:** Alport's syndrome is due to a defect in:?

→ Type IV collagen

### Haemolytic uraemic syndrome

The presence of **thrombocytopenia** and evidence of **haemolysis** in association with **bloody diarrhoea** should make you think of haemolytic uraemic syndrome (HUS).

Haemolytic uraemic syndrome - classically caused by E coli 0157:H7

Haemolytic uraemic syndrome is generally seen in young children and produces a **triad of**:

- acute renal failure
- microangiopathic haemolytic anaemia
- thrombocytopenia with normal clotting.

### Causes

- **post-dysentery - classically E coli 0157:H7** ('verotoxigenic', 'enterohaemorrhagic') Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion. The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.
- tumours
- pregnancy
- ciclosporin, the Pill
- systemic lupus erythematosus
- HIV
- Inherited recurrent HUS has been described with both dominant and recessive patterns of inheritance

### Investigations

- full blood count: anaemia, ↓ Serum haptoglobins (which bind haemoglobin), thrombocytopaenia, **fragmented blood film**
  - The hallmark of HUS is the appearance of **schistocytes** (fragmented, deformed, irregular, or helmet shaped red cells) on the blood film.
- There is normal coagulation and fibrinogen.
- U&E: acute renal failure
- stool culture

**Major differential diagnosis is:**

1. Sepsis with DIC - **presents with abnormalities of clotting parameters.**
2. TTP - thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease.
  - Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.
  - Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.
  - In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

feature	HUS	TTP
Acute kidney injury	more severe	Less severe
Neurological symptoms	less common	More common

**Complications** include:

- Stroke, seizure and coma occur in 25% of patients
- Rarely pancreatitis, and
- Pleural and pericardial effusions.
- Approximately 5% of patients will develop end stage renal failure.

**Management**

- treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients
- the indications for plasma exchange in HUS are complicated.
  - As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea
- Non-steroidal anti-inflammatory drugs and anti-diarrhoeals should be avoided

**Prognosis**

- Most children recover spontaneously from the illness, but mortality may be high in the elderly.
- Unfortunately fatality rates from HUS remain high, at between 5 and 10%.

**MRCPUK- part-1- September 2012 exam:** H/O bloody diarrhea and dehydration + ↓Platelet , ↑WBC, ↑urea & creatinine. Given the likely diagnosis, which organism is the most likely cause?

→ ***E. coli***

**MRCPUK- part-1- May 2010 exam:** Feature of diarrhoea , lethargy & acute renal failure. There is a known local outbreak of *E coli* 0157:H7. Given the likely diagnosis, which one of the following investigation results would be expected?

→ **Fragmented red blood cells (Δ haemolytic uraemic syndrome )**

## Renal tubular defects

- **thick ascending limb of Henle's loop:**
  - Bartter syndromes are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride in the thick ascending limb of Henle's loop
- **distal convoluted tubule:**
  - Gitelman syndrome are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride due to defect of thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule
- **proximal tubule:**
  - Carbonic anhydrase is expressed in the proximal tubule and is inhibited by acetazolamide; this is manifested biochemically by normal anion-gap metabolic acidosis
  - Fanconi syndrome refers to a proximal tubular defect that results in wasting of phosphate, calcium and amino acids .
    - seen in:
      - cystinosis
      - myeloma kidney
      - Wilson's disease
- **collecting ducts :**
  - Aquaporin channels are expressed in the cortical collecting ducts and are involved in water handling;
  - defects result in diabetes insipidus

You may find it useful to remember the location of the nephron defects in these conditions as being alphabetical, i.e. **B**artter affects the thick ascending limb, **G**itelman affects distal tubule and **L**iddle syndrome affects the collecting ducts. **BGL** is in alphabetical order, as is the order of the affected location in the nephrons.

## Fanconi syndrome

### Pathophysiology

- **Autosomal recessive**
- **Generalised dysfunction of the proximal tubule**, with the resultant urinary loss of bicarbonate, calcium, phosphate, urate, amino acids, glucose, and other organic acids and bases.
- The proximal convoluted tubule cells are unable to reabsorb HCO<sub>3</sub><sup>-</sup> leading to increased HCO<sub>3</sub><sup>-</sup> excretion in the urine → Type 2 (proximal) renal tubular acidosis (RTA)

### Causes

- Inherited disorders
  - ⇒ **Cystinosis** (**most common** cause in children)
  - ⇒ **Wilson's disease**
  - ⇒ Type 1 glycogen storage disease
- Sjogren's syndrome
- Multiple myeloma
- Nephrotic syndrome
- **Drugs:** e.g. **Rifampicin** , Expired tetracycline antibiotics, aminoglycosides
- Heavy metal poisoning (e.g., lead, cadmium, mercury)
- Ischemia (acute tubular necrosis)
- Amyloidosis
- Vitamin D deficiency
- Paroxysmal nocturnal haemoglobinuria

**Feature**

- Polyuria, **aminoaciduria**, Glucosuria despite normal or low serum glucose
- Phosphaturia → Hypophosphatemia
- Hypouricemia
- In children → growth retardation, renal rickets
- Metabolic acidosis**
- Osteomalacia

**Treatment**

- Replacement of lost electrolytes including potassium, phosphate, bicarbonate.
- Treatment of the cause

**Fanconi syndrome**

- Renal proximal convoluted tubular dysfunction.
- Symptoms: Failure to thrive (poor growth), hypokalaemia (muscle weakness or spasms, fatigue, palpitations), and hypophosphatemia (rickets, abnormal growth).

**Bartter and Gitelman syndromes****Definition**

- Bartter and Gitelman syndromes are an autosomal recessive renal tubular defects result in hypokalemic salt-losing (ie, salt-wasting).

**Pathophysiology**

- Gitelman syndrome: a loss of function mutation defect in thiazide-sensitive Na-Cl cotransporter in the **distal convoluted tubule**
- Bartter syndrome: a loss of function mutation defect in sodium chloride reabsorption in the **thick ascending limb of Henle's loop (NKCC2)**
- Hypokalemia, hypochloraemic metabolic alkalosis, polyuria, low to normal blood pressure, all result from **impaired sodium chloride reabsorption**.
- Renal biopsy → **Hyperplasia of the juxtaglomerular apparatus is characteristic**

**Similar features (both Bartter and Gitelman)**

- Often asymptomatic
- fatigue, cramps and weakness.
- Salt craving, thirst, polydipsia, polyuria and nocturia.
- Normotensive hypokalaemic metabolic alkalosis
- ↑sodium loss in the urine → volume depletion, → ↑serum renin and aldosterone → potassium loss in the urine

**Different features (which may differentiate Bartter from Gitelman)**

- Gitelman:**
  - ⇒ most common,
  - ⇒ present in adolescence and early adulthood,
  - ⇒ has milder symptoms,
  - ⇒ pseudogout
  - ⇒ **hypocalciuria**
  - ⇒ severe hypomagnesemia.
- Bartter:**
  - ⇒ present in children or early adolescence,
  - ⇒ has more severe symptoms,
  - ⇒ sensorineural deafness

- ⇒ hypercalciuria and normal or mild hypomagnesemia.
- ⇒ increased prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production

### Diagnosis approach

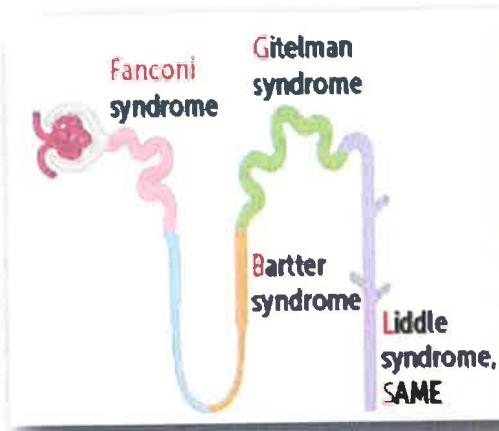
- **Step 1: suspicion:** Bartter or Gitelman syndrome should be suspected in any patient with unexplained hypokalemia, metabolic alkalosis, and a normal or low blood pressure.
- **Step 2 : exclude other more common causes** of these findings, in particular diuretic and/or laxative abuse and surreptitious vomiting → Urine diuretic screen.
- **Step 3:** spot urine chloride (repeated several times)
  - ⇒ consistently high (>20 mEq/L) in Bartter and Gitelman syndromes.
  - ⇒ consistently low (<20 mEq/L) with vomiting
  - ⇒ fluctuates between low and high with intermittent (and surreptitious or denied) diuretic use (high when the diuretic effect is present and low when it dissipates).
- **Step 4:** genetic testing

### Distinguishing Bartter syndrome from Gitelman syndrome

	Gitelman syndrome	Bartter syndrome
Gene affected	SLC12A3	SLC12A1 (Bartter syndrome type I)
prevalence	1 in 40,000	1 in a million.
Site of defect	Thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule	Sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2)
Presentation	present in adolescence and <b>early adulthood</b> ( <b>milder</b> symptoms)	Most cases are discovered in <b>infancy or early adolescence</b> (more <b>severe</b> symptoms)
Concentrating and diluting abilities	Concentrating capacity normal/near normal and diluting capacity reduced	Concentrating capacity reduced and diluting capacity reduced
Urinary calcium	<b>Reduced (hypocalciuria)</b>	<b>Increased (hypercalciuria)</b>
Serum magnesium	<b>severe hypomagnesemia</b> is common	either <b>normal or mildly reduced</b>

### Treatment (for Bartter or Gitelman syndrome)

- First line: Electrolyte supplementation (sodium, potassium, and magnesium salts)
- Second line: Potassium-sparing diuretics that inhibits distal sodium-potassium exchange, such as spironolactone, eplerenone, or amiloride.
- Third-line: NSAIDs or ACE inhibitors



### Locations of renal tubular defects

SAME: Syndrome of Apparent Mineralocorticoid Excess

The effects of **Gitelman syndrome** are similar to those of a **thiazide diuretic**.

The effects of **Bartter syndrome** are similar to those of a **loop diuretic**. Loop diuretics work by inhibiting NKCC2- Think of Bartters syndrome as like taking large dose of furosemide.

**Gitelman's syndrome:** Normotensive hypokalaemic metabolic alkalosis **with Hypocalciuria and significant hypomagnesaemia.**

**Bartter syndrome:** Normotensive hypokalaemic metabolic alkalosis **with hypercalciuria, normal or mild hypomagnesaemia, metabolic alkalosis.**

The hypokalemia with normal blood pressure in a **middle aged male without any skeletal abnormalities or retardation** would suggest a diagnosis of **Gitelman syndrome** rather than Bartter's syndrome.

## Renal tubular defects

	<b>Causes</b>	<b>Defect</b>	<b>Effect</b>	<b>Note</b>
<b>Bartter syndrome</b>	Autosomal recessive	Reabsorption defect in thick ascending loop of Henle (affects $\text{Na}^+/\text{K}^+$ - $/2\text{Cl}^-$ cotransporter)	Normotensive hypokalaemic metabolic alkalosis <b>hypercalciuria</b>	Presents similarly to chronic loop diuretic use
<b>Gitelman syndrome</b>	Autosomal recessive	Reabsorption defect of $\text{NaCl}$ in distal convoluted tubule	Normotensive hypokalaemic metabolic alkalosis, <b>hypomagnesemia,</b> <b>hypocalciuria</b>	Presents similarly to life-long thiazide diuretic use Less severe than Bartter syndrome
<b>Liddle syndrome</b>	<b>Autosomal dominant</b>	Gain of function mutation → ↓ $\text{Na}^+$ channel degradation → ↑ $\text{Na}^+$ reabsorption in collecting tubules	<b>Hypertensive</b> hypokalaemic metabolic alkalosis, ↓ <b>aldosterone</b>	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable. Treatment: amiloride
<b>Fanconi syndrome</b>	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (eg, cisplatin), lead poisoning	Generalized reabsorption defect in PCT excretion of amino acids, glucose, $\text{HCO}_3^-$ , and $\text{PO}_4^{3-}$ , and all substances reabsorbed by the PCT	Hypokalemic metabolic acidosis (proximal RTA), <b>hypophosphatemia</b>	Growth retardation and rickets/osteopenia common due to hypophosphatemia Volume depletion also common
<b>Syndrome of Apparent Mineralocorticid Excess (SAME)</b>	Autosomal recessive OR acquired from glycyrrhetic acid (present in liquorice), which blocks activity of 11 $\beta$ -hydroxy steroid dehydrogenase	Cortisol activates mineralocorticoid receptors; 11 $\beta$ -HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11 $\beta$ -HSD deficiency → ↑cortisol → ↑mineralocorticoid receptor activity	<b>Hypertensive</b> hypokalaemic metabolic alkalosis, ↓ <b>aldosterone</b> , <b>Cortisol tries to be the SAME as aldosterone</b>	Treatment: K+-sparing diuretics (↓mineralocorticoid effects) or corticosteroids (exogenous corticosteroid → ↓endogenous cortisol production → ↓mineralocorticoid receptor activation)

## Liddle's syndrome

### **Pathophysiology**

- **Autosomal dominant** (gain of function mutation) → ↑ activity of Epithelial Sodium Channels (ENaC) → ↑ reuptake of water and sodium → activation of sodium/potassium exchange independent of circulating mineralocorticoid (**pseudohyperaldosteronism**).

### **Diagnostic features**

- Hypertension
- Hypokalaemia
- Metabolic alkalosis
- Decreased renin and aldosterone levels

### **Treatment**

- **Amiloride**: Potassium-sparing diuretics: acts directly on the sodium channel → (epithelial sodium channel (ENaC) antagonists)
- **Spironolactone is not an effective treatment** as the increased activity of the ENaC is not mediated by aldosterone.

### **Top Tips**

Liddle's syndrome: hypokalaemia + hypertension

**hypokalaemic alkalosis + suppressed renin and aldosterone + hypertension → Liddle's syndrome**

**The clinical features of Liddle syndrome are similar to those of hyperaldosteronism, except that Liddle syndrome manifests with decreased renin and aldosterone levels.**

## Glomerulonephritides

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

### **Membranous glomerulonephritis**

- presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

### **IgA nephropathy - aka Berger's disease, mesangiproliferative GN**

- typically young adult with haematuria following an URTI

### **Diffuse proliferative glomerulonephritis (DGN)**

Diffuse proliferative glomerulonephritis, causes:

- post-streptococcal
- SLE

Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- The following features are supportive of diagnosis:
  - haematuria
  - proteinuria
  - oedema
  - hypertension
- **most common form of renal disease in SLE**
- In DPGN, **more than 50% of the glomeruli** (diffuse) show an increase in mesangial, epithelial, endothelial (proliferative), and inflammatory cells (ie, glomerulonephritis). (Increased cellularity)
- when < 50% of the glomeruli are involved, the condition is termed focal proliferative glomerulonephritis. However, this entity has the potential to progress to DPGN.

#### **Minimal change disease**

- typically a child with nephrotic syndrome (accounts for 80%)
- causes: Hodgkin's, NSAIDs
- good response to steroids

#### **Focal segmental glomerulosclerosis**

- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

#### **Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis**

- rapid onset, often presenting as acute kidney injury
- causes include Goodpasture's, ANCA positive vasculitis

#### **Mesangiocapillary glomerulonephritis (membranoproliferative)**

- type 1: cryoglobulinaemia, hepatitis C → associated with low C4
- type 2: partial lipodystrophy → associated with low C3
- C3 nephritic factor is an autoantibody specific for alternative pathway C3 convertase (C3NeF), found in mesangiocapillary GN type II and partial lipodystrophy.

#### **Diagnosis**

- **Renal biopsy is the best investigation to diagnose Glomerulonephritis**
- **RBC casts in urinary sediment suggest a diagnosis of acute glomerulonephritis (Acute nephritic syndrome)**

- Immune complex glomerulonephritides can be classified based on normal or decreased C<sup>3</sup>.
  - **Associated with reduced C<sup>3</sup> and C<sup>4</sup>**
    - Cryoglobulinaemia
    - Infective endocarditis
    - lupus nephritis
  - **Associated with reduced C<sup>3</sup>.**
    - membranoproliferative GN
    - post-streptococcal GN

**Glomerulonephritis and low complement**

Disorders associated with glomerulonephritis and low serum complement levels:

1. post-streptococcal glomerulonephritis
2. subacute bacterial endocarditis
3. systemic lupus erythematosus
4. mesangiocapillary glomerulonephritis

**MRCPUK-part-1-May 2014 exam: A patient of SLE present with pedal oedema , ↑ BP.**

**Dipstick urine shows protein ++, blood+++. What is the renal biopsy most likely to show?**

- **Diffuse proliferative glomerulonephritis** (Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients.)

**Minimal change disease**

Minimal change glomerulonephritis - prednisolone

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

**Epidemiology**

- accounting for 75% of cases in children and 25% in adults.
- peak incidence 2-3 years of age

**Causes**

- 90% of cases are idiopathic
- Other causes (10 – 20%)
  - drugs: NSAIDs, rifampicin **gold** and lithium
  - **Hodgkin's lymphoma**, thymoma
  - infectious mononucleosis

**Pathophysiology**

- **The glomerular basement membrane is normal on electron microscopy**
- T-cell and cytokine mediated damage to the glomerular basement membrane → polyanion loss
- the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin

**Features**

- nephrotic syndrome
  - nearly always presents as nephrotic syndrome
- normotension
  - hypertension is rare (only 10%)
- **highly selective proteinuria\*** (\*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus)
  - ⇒ A protein selectivity index of less than 10% is highly selective and is a ratio of serum and urine IgG and albumin.
  - ⇒ High selectivity suggests minimal change disease but is less reliable in adults.
- **Renal biopsy:**
  - **light microscopy** are normal or small looking glomeruli
  - **electron microscopy** shows fusion of podocytes

- (Effacement of the epithelial cell foot processes over the outer surface of the GBM)
- renal biopsy is not indicated unless no response to steroids is seen within one month, there is hypertension, haematuria or renal impairment.
  - renal biopsy is usually only attempted when three or more episodes of oedema have occurred.

**Podocytes fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common**

### Management

- majority of cases (80%) are steroid responsive
  - shows excellent response to steroids since the damage is mediated by T-cell cytokines.
- cyclophosphamide is the next step for steroid resistant cases
  - Immunosuppression treatment (cyclophosphamide) should be considered in patients who are **frequent relapsers (two or more episodes in six months of the initial response, or four relapses in any one year)**, children who are steroid dependent or steroid toxic).

### Prognosis

is overall good

- **Remission: Full renal recovery is the most likely outcome.**
  - **In Children:**
    - 30 – 40% of children achieve spontaneous remission
    - and 90% achieve remission following eight weeks treatment with high dose steroids.
  - **In adults** only around 50% achieve remission.
- **Relapse** is common. Roughly:
  - 1/3 have just one episode
  - 1/3 have infrequent relapses
  - 1/3 have frequent relapses which stop before adulthood

## Membranous glomerulonephritis

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

- **Membranous glomerulonephritis is the commonest type of glomerulonephritis in adults** and is the third most common cause of end-stage renal failure (ESRF).
- It usually presents with nephrotic syndrome or proteinuria.
- It is an antibody mediated disease in which the immune complexes localise to the subepithelial aspect of the capillary loop. That is, between the outer aspect of the basement membrane and the podocyte (epithelial cell).
- **Males are twice as commonly affected as females**
- Typically seen in the over 40 age group (Elderly patients)
- Most patients have normal blood pressure at the time of the presentation.

- Most of the patients with membranous glomerulonephritis have antibodies against M-type phospholipase A2 receptor.

### Causes

- idiopathic
- infections: **hepatitis B**, hepatitis C , **malaria**, syphilis , leprosy, HIV, schistosomiasis,
- malignancy**: lung cancer, **non-Hodgkin's lymphomas lymphoma**, leukaemia, **colon** and gastric cancer
  - (30% of membranous nephropathy cases are secondary, of those around a third (10% of the total cases of membranous nephropathy) are diagnosed with an underlying malignancy)
  - (NOTE: In the case of **Hodgkin's lymphoma**, the most common histological type of renal involvement is **minimal change** glomerulonephritis followed by focal segmental glomerulosclerosis).
- drugs: gold, **penicillamine**, NSAIDs , captopril, and heavy metals: mercury and cadmium
- autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid
- Sickle cell disease.
- Diabetes mellitus.

### Renal biopsy demonstrates:

- light microscopy:
  - diffuse capillary and glomerular basement membrane thickening.
- electron microscopy:
  - the basement membrane is thickened with subepithelial electron dense deposits (**Thickened capillary loops**). This creates a 'spike and dome' appearance
- Immune complex
  - deposition with IgG and C3**

### Complications

- Renal vein thrombosis is particularly likely to complicate membranous glomerulonephritis**
  - As the left testicular vein drains into the left renal vein, a left-sided varicocele may develop in this condition.

### Prognosis

- Rule of thirds
  - one-third: spontaneous remission
  - one-third: remain proteinuric
  - one-third: develop ESRF
- Good prognostic features include:
  - female sex
  - young age at presentation and
  - asymptomatic proteinuria of a modest degree at the time of presentation.

### Management:

- Immunosuppression: corticosteroids alone have not been shown to be effective.
- A combination of corticosteroid + another agent such as chlorambucil is often used
  - Cyclophosphamide plus methylprednisolone is the most appropriate management**
- blood pressure control: ACE inhibitors have been shown to reduce proteinuria

- Ramipril is proven to affect both proteinuria and hypertension in patients with a diagnosis of membranous nephropathy, and is therefore the most likely treatment to affect the patient's prognosis
- consider anticoagulation
- Approximately 30% of cases are secondary to other conditions, and in those cases treatment of the underlying cause may be curative.

**MRCPUK-part-1-September 2011 exam:** H/O colorectal cancer developed 'frothy' urine. The results suggest nephrotic range proteinuria. Assuming the proteinuria is related to his **colorectal cancer** what is the renal histology most likely to show?

→ Membranous glomerulonephritis

**MRCPUK-part-1-May 2012 exam:** H/O peripheral oedema with no past medical history of note. His urinary protein is 4.2g/24 hours. BP is 160/92 mmHg. A renal biopsy shows: thickened capillary walls & Subepithelial deposits. Given the likely diagnosis, which one of the following drugs is most likely to be beneficial?

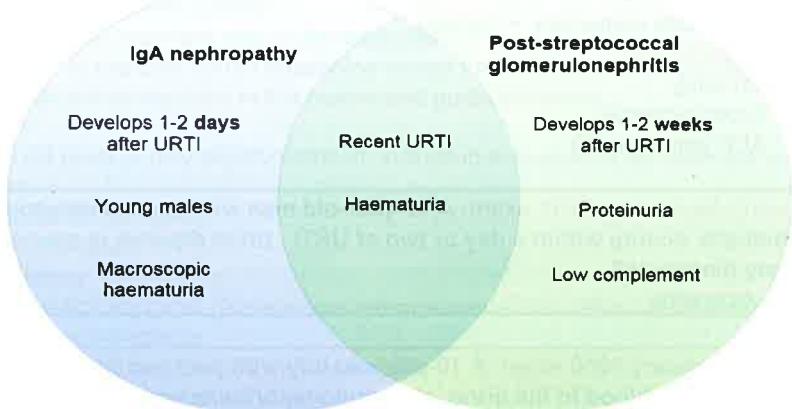
→ ACE inhibitor (Δ membranous glomerulonephritis)

## IgA nephropathy

### Basics

- also called Berger's disease or mesangioliferative glomerulonephritis
- **commonest cause of glomerulonephritis worldwide**
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- Has a male preponderance
- **commonly diagnosed in the age range of 20-40.**

Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis



- post-streptococcal glomerulonephritis is associated with low complement levels
- main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)
- there is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis

### Presentations

- young male, recurrent episodes of macroscopic haematuria
- Haematuria occurs within 12-24 hours of pharyngitis,

- typically associated with mucosal infections e.g., URTI , or less commonly infection of other mucous membranes (e.g. GI, bladder, breast).
- accompanied also by loin pain, muscle pain and fever.
- nephrotic range proteinuria is rare
- The majority of patients have normal renal function.
- renal failure

#### Associated conditions

- Alcoholic** cirrhosis (**Alcohol excess**) (**haematuria + alcohol excess → IgA nephropathy**).
- coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

#### Diagnosis

- Renal biopsy** is the investigation of choice to confirm the diagnosis
  - **histology: Mesangial hypercellularity**,
  - positive immunofluorescence for **IgA** & C3

#### Management

- No specific treatment is available. **Observation is the most appropriate management**
- steroids/immunosuppressants not be shown to be useful.
  - Treatment with corticosteroids is usually reserved for those patients with hypertension and a rising creatinine.
- When there is nephrotic range proteinuria (>3 g/day) an 8-12 week course of prednisolone should be prescribed.
- If the proteinuria is <3 g/day an ACE inhibitor can be used.

#### Prognosis

- 30% of children will have a spontaneous remission within 10 years
- 25% of patients develop ESRF within 20 years
- markers of good prognosis: frank haematuria
- markers of poor prognosis:**
  - male gender,
  - proteinuria (especially > 2 g/day),
  - **hypertension**
  - smoking,
  - hyperlipidaemia,
  - ACE genotype DD

**MRCPUK-part-1-September 2011 exam:** A 17-year-old man with several episodes of visible haematuria, occurs within a day or two of URTI . Urine dipstick is normal. What is the most likely diagnosis?

→ **IgA nephropathy**

**MRCPUK-part-1-January 2006 exam:** A 10-year-old boy with past two days H/O sore throat associated with blood in his urine. glomerulonephritis is suspected. What would a renal biopsy most likely show?

→ **Mesangial hypercellularity** (Δ IgA nephropathy)

**MRCPUK-part-1-September 2007 exam:** A 12-year-old boy with purpuric rash on the extensor surfaces of his lower legs + abdominal pain and an urticarial rash. Urine dipstick reveals blood ++.What would be the likely finding on renal biopsy?

→ **Mesangial hypercellularity** (Henoch-Schonlein purpura is associated with IgA nephropathy)

**MRCPUK-part-1-January 2014 exam:** A 19-year-old woman C/O painless visible haematuria, occur within a day or two of developing tonsillitis. BP is 148/90 mmHg. Given the likely diagnosis, which marker indicate poor prognosis?

→ Hypertension (Δ IgA nephropathy)

**MRCPUK-part-1-September 2007 exam:** Which one of the following is associated with a better prognosis in patients with IgA nephropathy?

→ Frank haematuria

## Post-streptococcal glomerulonephritis

### Overview

- Also known as **acute proliferative glomerulonephritis**
- typically occurs 7-14 days following a group A beta-haemolytic *Streptococcus* infection (usually *Streptococcus pyogenes*).
  - Acute glomerulonephritis can be caused by both pharyngeal and skin infections with group A beta-haemolytic *Streptococcus*, but only pharyngeal infections typically lead to acute rheumatic fever.
- caused by immune complex (IgG, IgM and C3) deposition in the glomeruli.
- type III hypersensitivity reaction.

### Epidemiology

- Young children most commonly affected.

### Features

- general: headache, malaise
- haematuria
  - Dark-colored urine is often a presenting sign.
- nephritic syndrome
- hypertension

### Investigations

- BMP (Basic metabolic panel)**
  - the most important step in the diagnosis
  - BMP to evaluate serum **creatinine** kidney function is ideal to determine the level of glomerulonephritis in this patient and guide treatment.
- low C3**
- normal C4 level** or only slightly reduced, indicating activation of the alternate complement pathway
- Depressed CH 50 level**
- Raised ASO titer**
- Renal biopsy**
  - post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis
  - endothelial proliferation with neutrophils
  - electron microscopy:
    - subepithelial 'humps' caused by lumpy immune complex deposits.
    - The hump-like appearance in subepithelial space is characteristic of post-streptococcal glomerulonephritis.**
    - 'Lumpy-bumpy' appearance on immunofluorescence is characteristic.**
  - immunofluorescence:
    - granular or 'starry sky' appearance
    - There is antibody and compliment deposition on immunostaining.

- light microscopy
  - 'wire-loop' lesions on light microscopy.

#### Treatment

- Patients with acute proliferative glomerulonephritis presenting with hypertension are managed with loop diuretics.

#### Prognosis

- **Carries a good prognosis**
- **Age is the most important prognostic factor** in post-streptococcal glomerulonephritis.
  - 95% of affected children recover completely, compared with 25% of adults over 60 years old.

## Membrano-proliferative glomerulonephritis (MPGN).

Membranoproliferative glomerulonephritis (mesangiocapillary)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

#### Overview

- also known as **mesangio-capillary** glomerulonephritis(MCGN),
- more recently been termed **complement mediated** glomerulonephritis.

#### Associations

- It is associated with SLE, cryoglobulinaemia with or without **hepatitis C**, chronic infections (SBE) , neoplasms, hepatitis B, schistosomiasis, malaria and leprosy.

#### General features

- may present as nephrotic syndrome, haematuria or proteinuria
- **Circulating immune complexes are seen**
- Classically associated with decreased serum C3 (and a normal C4, indicating activation of the alternative pathway of complement).
- Hypocomplementemia (Low C3 levels) is a characteristic finding with all types of (MPGN).
- appears on light microscopy with "tram-track" capillary loops of glomerular basement membranes.

#### Type 1

- **Epidemiology**
  - accounts for 90% of cases
- **histology**
  - **sub-endothelial immune deposits** of electron dense material, **Thickening and splitting of the capillary basement membrane** (double layer of glomerular basement membrane), resulting in a '**tram-track**' appearance
- Causes:
  - cryoglobulinaemia (→ **low C3**),
  - **hepatitis C**
    - ❖ (hepatitis C is endemic among the iv drug-users).
    - ❖ Hepatitis C is now considered the principal cause of 'idiopathic' mesangiocapillary glomerulonephritis (MCGN).

#### Type 2

- Also known as → Dense deposit disease
- causes:
  - **partial lipodystrophy**,
  - factor H deficiency,
  - may be idiopathic or

- may occur after measles
- Features
  - reduced serum complement
  - C3b nephritic factor (an antibody against C3bBb) found in 70% → low C3
- Histology
  - 'dense deposit'
  - characterised by mesangial cell proliferation with electron-dense,
  - linear intramembranous deposits that stain positive for C3 (**C3 nephritic factor**)

### Type 3

- Subepithelial and subendothelial deposits
- causes: hepatitis B and C

### Management

- steroids may be effective

### Prognosis

- poor prognosis

**MRCPUK-part-1-September 2009 exam:** patient of nephrotic syndrome is noted to have marked loss of subcutaneous tissue from the face. What is the most likely underlying cause of her renal disease?

→ Membranoproliferative glomerulonephritis type II (Δ partial lipodystrophy)

**MRCPUK-part-1-September 2009 exam:** A patient develops membranoproliferative glomerulonephritis secondary to partial lipodystrophy. Which type of complement is likely to be low?

→ C3

## Rapidly progressive glomerulonephritis (RPGN)

Rapidly progressive glomerulonephritis, causes:

- Goodpasture's
- ANCA positive vasculitis

### Overview

- rapid loss of renal function associated with the formation of epithelial **crescents** in the majority of glomeruli.
- results in a rapid decrease in GFR of at least 50% over a short period (a few days to 3 months).
- The most aggressive GN, with potential to cause ESRF over days.

### Causes

- |                            |  |
|----------------------------|--|
| • Goodpasture's syndrome   | • others: SLE, microscopic Polyarthritis |
| • Wegener's granulomatosis | • <b>secondary syphilis</b>              |

### Types

#### 1. Type I RPGN (~3%):

- Serum anti-glomerular basement membrane (Anti-GBM) antibody is positive.
- Antibody deposits along the glomerular basement membrane in a linear fashion.
- Example: Goodpasture syndrome.

#### 2. Type II RPGN: Immune complex disease (~45% of cases):

- (Anti-GBM) antibody is negative,

- but irregular immune complex (antibody-antigen) deposits are found within the glomeruli.
- Example: lupus nephritis and post-streptococcal glomerulonephritis.

3. **Type III RPGN:** (**Pauci-immune** disease (~50% of cases, 80–90% ANCA +ve):
  - Serum anti-neutrophil cytoplasmic (ANCA) antibodies are positive.
  - Negative immunofluorescence.
  - Example: **Wegener** granulomatosis and microscopic polyangiitis.

### Features

- nephritic syndrome: haematuria with red cell casts, proteinuria, hypertension, oliguria
- features specific to underlying cause (e.g. haemoptysis with Goodpasture's, vasculitic rash or sinusitis with Wegener's)

### Investigations

- Immunofluorescence detects deposits of IgG and C3 in the glomerular BM
- The main pathological finding is **fibrinoid necrosis** > 90% of biopsy specimens with extensive **crescent formation** in at least 50% of the glomeruli. These crescents are collections of epithelial cells and macrophages proliferation within the Bowman's space.

### Treatment

- Aggressive immunosuppression with high-dose IV steroids and cyclophosphamide
- +/- plasma exchange.

### Prognosis:

- 5-year survival 80%.

**MRCPUK-part-1-January 2012 exam:** H/O chronic sinusitis, haemoptysis and microscopic haematuria. cANCA (PR3)= Positive. Given the likely diagnosis, what findings would be expected on renal biopsy?

→ **Crescentic glomerulonephritis**

## Focal segmental glomerulosclerosis (FSGS)

### Overview

- cause nephrotic syndrome and chronic kidney disease.
- In FSGS, as the name suggests, only some glomeruli are affected (focal) and just some of the affected glomeruli are diseased (segmental).
- **cholesterol levels rise** due to increased cholesterol synthesis in the liver and the loss of lipid-regulating proteins in urine

### Epidemiology

- generally presents in young adults.
- the second most common cause of nephrotic syndrome in adults, after membranous glomerulonephritis (GN)
- The most common cause of nephrotic syndrome in Hispanic and **African-Americans**
- Incidence: 40% in adults. 20% in children

### Pathophysiology

- Caused by an injury to **podocytes** in the renal glomeruli.

### Causes

- idiopathic (in 80%)
- secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- **HIV** → **'collapsing glomerulopathy'**
  - The most common type of (HIV-associated nephropathy) is a collapsing (FSGS).
- intravenous drug use

- heroin
- Alport's syndrome
- sickle-cell
- associated with severe obesity
- medications:
  - Interferon alfa, lithium, sirolimus, and pamidronate.

### Histology

- histology may appear normal and may be confused with minimal change nephropathy
- deep glomeruli at the corticomedullary junction are affected first, these may be missed on transcutaneous biopsy, leading to a mistaken diagnosis of a minimal change glomerular lesion
- light microscopy
  - Segmental sclerosis and hyalinosis
- Immunofluorescence microscopy
  - usually unremarkable.
  - Immunofluorescence is negative because there is no antibody or immune complex deposition.
  - biopsy will show partial scarring of the glomerulus with no immunofluorescence.
- Electron microscopy
  - The hallmark pathologic feature is podocyte foot processes fusion.
  - can distinguish primary from secondary FSGS. Foot process fusion is diffuse in primary FSGS but is mostly limited to sclerotic areas in secondary FSGS.
- fibrinogen are deposited in juxamedullary capillaries

### Treatment

- 50% of (FSGS) do not respond to steroid
- The first line of management is glucocorticoids.
- (ACE) inhibitors are a recognised strategy to slow the progression of renal disease.

### Prognosis

- It leads to chronic renal failure in 50% of cases.
- typically progresses to renal failure over a 6–8 year period.
- 2% of dialysis patients have FSGS.
- **have a high recurrence rate in renal transplants**
  - FSGS recurs in 40% of renal transplants

**January 2011 exam:** A patient with H/O heroin abuse, his creatinine = 156, urine show = ++ protein. What is the most likely cause of his deteriorating renal function?

→ **Focal segmental glomerulosclerosis** (Heroin is a known cause of focal segmental glomerulosclerosis)

## Goodpasture's syndrome

### Goodpasture's syndrome

- IgG deposits on renal biopsy
- anti-GBM antibodies

**Goodpasture's syndrome is characterised by pulmonary haemorrhage and crescentic glomerulonephritis.**

**Definition**

- Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis.

**Epidemiology**

- more common in men (sex ratio 2:1)
- has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket).

**Genetics**

- associated with **HLA DR2**
- p-ANCA positive in 30% and is directed against myeloperoxidase.

**Pathophysiology**

- It is a type II cytotoxic reaction caused by anti-glomerular basement membrane (anti-GBM) **antibodies against the  $\alpha$  3 chain of type IV collagen** (basement membrane of both the kidneys and lungs).
- Goodpasture syndrome is due to **IgG antibodies produced against the basement membrane causing damage via a type II hypersensitivity reaction**.

**Features**

- pulmonary haemorrhage
  - respiratory symptoms can vary from minimal **hemoptysis** to massive **alveolar hemorrhage**, leading to respiratory failure. In lungs, this is a **type 2 hypersensitivity** reaction.
    - Hemoptysis is a clinical feature of Goodpasture's syndrome **due to cross reaction of anti-glomerular basement membrane antibodies** at the lungs.
  - cough
  - Fever
- followed by rapidly progressive glomerulonephritis (RPGN) (Renal impairment is caused by a **crescentic glomerulonephritis**)
  - haematuria
  - proteinuria, and
  - red cell casts.

**Factors which increase likelihood of pulmonary haemorrhage**

- normally, the alveolar epithelium prevents contact of antibody with basement membrane collagen, thus any **condition that increases permeability of alveoli** can cause triggering of this syndrome. Such susceptibility factors include:
  - smoking
  - lower respiratory tract infection
  - pulmonary oedema
  - inhalation of hydrocarbons and toxic gases
- young males

**Investigations**

- **serological testing** (for anti-GBM antibodies)
- **biopsy** from kidney rather than lung.
  - Renal biopsy:
    - **linear IgG deposits along basement membrane** (the most likely finding on renal biopsy → **Linear immunofluorescence**)
  - Lung biopsy
    - linear staining of IgG along the alveolar capillary basement membranes

- disruption of alveolar septa and **haemosiderin-laden macrophages** because there may be pulmonary haemorrhage associated with the condition.
- raised transfer factor secondary to pulmonary haemorrhages.
- Serial measurement of carbon monoxide (CO) diffusing capacity or transfer factor (Tlco) can be used to monitor progression,

### Management

- General management
  - **ABC**
    - **If the patient is hypoxic → intubate and mechanically ventilate the patient.**
    - Patients should not smoke and should avoid hydrocarbon exposure.
- **The most appropriate initial management → IV methylprednisolone and cyclophosphamide**
- plasma exchange (**plasmapheresis**)
  - Where there is severe haemoptysis, rapid removal of anti-GBM antibody is indicated, and the best way to do this is by plasmapheresis **at a specialist centre**.
  - This is usually accompanied by pulsed therapy with IV methylprednisolone and cyclophosphamide.
- steroids
- cyclophosphamide
  - Response is assessed by monitoring symptoms and anti-GBM antibody titres.
  - Cyclophosphamide and prednisolone continued, typically for 6 - 9 months following remission.

**In the acute setting**, treatment is focused on:

1. managing life threatening complications of renal failure, such as hyperkalaemia → haemodialysis.
2. Removing the circulating auto-antibody responsible for disease → **plasmapheresis** (therapeutic plasma exchange),
  - **the most important management step in the next few days after haemodialysis**

### Prognosis:

- Despite treatment, the **mortality** of Goodpasture's is 11% and it has a high **morbidity** with 60% of patients becoming dependent on dialysis.
- In practice, glomerulonephritis proves to be a much commoner threat to survival than lung haemorrhage,

### Other causes of raised anti-GBM antibody levels:

- Some healthy individuals exposed to inhaled oils, hydrocarbons or solvents can have borderline raised anti-GBM antibody levels.
- Anti-GBM antibodies have also been detected in HIV-negative patients with Pneumocystis pneumonia.

## Nephrotic syndrome

Triad of:

- 1. Proteinuria ( $> 3\text{g}/24\text{hr}$ ) (The minimum proteinuria which is defined as 'nephrotic' is **300 mg/mmol**) causing →
- 2. Hypoalbuminaemia ( $< 30\text{g/L}$ ) and
- 3. Oedema

Other features:

- **Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis.**
- Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels.
- **Increased serum cholesterol**
  - $\uparrow(\text{LDL})$ 
    - LDL and VLDL are removed from serum by lipoprotein signals. If the lipoprotein is lost in the urine with nephrotic syndrome, then the lipid levels in the blood rise.
  - **HDL is usually normal**
- $\downarrow\downarrow \text{Ca} \& \text{vit D}$  (loss of 25-hydroxyvitamin D3 (25OHD3) in the urine → hypocalcaemia)
- Serum C3 levels are decreased in immune complex-mediated glomerulonephritis

	<b>Nephrotic</b>	<b>Nephritic</b>
<b>Common primary causes</b>	Membranous Minimal change FSGS Mesangiocapillary GN	IgA nephropathy Mesangiocapillary GN
<b>Common secondary causes</b>	Diabetes SLE (class V nephritis) Amyloid Hepatitis B/C	Post streptococcal Vasculitis SLE (other classes of nephritis) Anti-GBM disease (Figs 1 & 2) Cryoglobulinaemia
<b>BP</b>	Normal–mild $\uparrow$	Moderate–severe $\uparrow$
<b>Urine</b>	Proteinuria $> 3.5\text{g/day}$	Haematuria (mild–macro)
<b>GFR</b>	Normal–mild $\uparrow$	Moderate–severe $\downarrow$

### Causes

#### **Nephrotic syndrome - malignancies cause membranous glomerulonephritis**

- glomerulonephritis accounts for around 80% of cases
  - minimal change glomerulonephritis (causes 80% in children, 30% in adults)
  - membranous glomerulonephritis
  - focal segmental glomerulosclerosis (FSGS).
    - Patients presenting with **isolated heavy proteinuria without the other components of nephrotic syndrome** is more likely due to (FSGS).
- Systemic disease (about 20%)
  - diabetes mellitus
    - (Diabetic nephropathy often presents as nephrotic syndrome but typically develops at least 15 years after onset).
  - systemic lupus erythematosus
  - amyloidosis (in patient with chronic inflammatory state , amyloidosis is the likely cause of NS)

- Drugs
  - gold (sodium aurothiomalate), penicillamine
- Others
  - congenital
  - neoplasia: carcinoma, lymphoma, leukaemia, myeloma
    - Chronic lymphocytic leukemia (CLL) and Non-Hodgkin's lymphoma (NHL) are the most common hematologic malignancies associated with glomerular diseases.
    - Membranoproliferative glomerulonephritis (MPGN) are most common glomerular disease associated with CLL and NHL
    - the most common renal lesion associated with Hodgkin's disease is minimal change disease
  - infection: bacterial endocarditis, hepatitis B, malaria (**commonly plasmodium malariae**)

### Investigations

- **Renal biopsy**
- *Contraindications for renal biopsy:*
  - Abnormal clotting
  - Hypertension >160/90mmHg
  - **Single kidney** (except for renal transplants)
  - Chronic kidney disease with small kidneys (<9cm)
  - Uncooperative patient
  - Horseshoe kidney
  - Renal neoplasms.

### Serum electrophoresis in nephrotic syndrome

- ↑ **serum α- and β-globulin fractions.** (The increase in globulin fractions is thought to occur due to increased synthesis in patients with urinary protein loss)
  - **Increased α<sub>1</sub> and α<sub>2</sub>-globulin fractions, decreased serum albumin**
- A monoclonal paraprotein band will be present where myeloma is the underlying cause,
- there may be associated immune paresis with reduced concentrations of one or more of the immunoglobulins IgG, IgA or IgM

### Complications

- increased risk of infection in particular pneumococcal infections **due to** urinary immunoglobulin loss and decreased splanchnic blood flow.
- **Increased risk of thromboembolism related to loss of antithrombin III** and plasminogen in the urine , increased fibrinogen and increased factor VIIIc. Renal vein thrombosis occurs in 15-20% of patients with nephrotic syndrome
  - **Renal vein thrombosis**
    - Occurs in 10-20%
    - Feature → often clinically silent , (loin pain + haematuria) and acute renal injury
    - Initial investigation → US (swollen oedematous kidney)
    - Diagnosis → Duplex US renal veins, CT or MRV
    - Treatment → long term anticoagulation.
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure
- **Intravascular volume depletion :**Hypoalbuminaemia results in decreased intravascular oncotic pressure, leading to leakage of extracellular fluid from blood to the interstitium

## Treatment

- In general, steroids are tried first and then second line agents such as cyclosporin and cyclophosphamide are introduced if needed.
- **Cyclophosphamide is the best treatment for steroid-dependent nephrotic syndrome**
  - No more than two courses of cyclophosphamide should be prescribed in children because of the risk of side effects, which include azoospermia
  - An alternative to cyclophosphamide is ciclosporin, which is effective but must be continued long-term to prevent relapse on stopping treatment. Ciclosporin is also potentially nephrotoxic

**MRCPUK-part-1-January 2006 exam:** What changes in patients with nephrotic syndrome predispose to the development of venous thromboembolism?

- Loss of antithrombin III

**Which finding would support a diagnosis of a protein losing enteropathy rather than nephrotic syndrome?**

- Low total cholesterol

- The pathophysiology of protein loss in protein-losing gastroenteropathy is different from that in glomerular diseases.
- ❖ **In glomerulopathies, protein loss is determined by molecular weight and charge.**
- ❖ By contrast, the leakage of individual serum proteins in patients with protein-losing gastroenteropathy is independent of molecular weight.
- For this reason, cholesterol levels are low, in contrast to nephrotic syndrome where cholesterol levels are high (due to the molecular weight of cholesterol).

## Analgesic nephropathy

- common in women , F : M = 2: 1 , and presents most often in middle age
- caused by non-steroidal anti-inflammatory drugs (NSAIDs) for **chronic pain or headache**,
- Characteristically, associated with phenacetin use, particularly in Australia and New Zealand
- features may include **anaemia**, chronic renal failure, **symptoms of urinary tract infection**, haematuria or hypertension.
- **Complications**
  - **Urinary tract malignancy** (8-10% of patients with analgesic nephropathy),
  - For example, in women under the age of 50 analgesic abuse is the most common cause of bladder cancer.

## Renal stones

### Renal stones on x-ray

- cystine stones: semi-opaque
- urate + xanthine stones: radio-lucent

### Stag-horn calculi

- composed of Struvite (ammonium magnesium phosphate, triple phosphate)
- form in alkaline urine (ammonia producing bacteria such as *Ureaplasma urealyticum* and *Proteus* therefore predispose)
  
- The most common stones are **calcium oxalate** stones followed by **calcium phosphate**.
- Calcium phosphate stones are seen in renal tubular acidosis (RTA).

### Risk factors

- dehydration
- hypercalciuria, hyperparathyroidism, hypercalcaemia
- cystinuria ( AR defect in dibasic amino acid transporter)
- high dietary oxalate. hyperoxaluria (for example, XS intake, ileal disease and bypass)
- renal tubular acidosis => (Calcium phosphate stones)
- medullary sponge kidney, polycystic kidney disease
- beryllium or cadmium exposure
- Chronic infection with urea splitting organisms: causes stones made of magnesium ammonium phosphate and calcium phosphate (infection stones (5%)
- Familial : Idiopathic hypercalciuria inherited as autosomal dominant whereas cystinuria, cystinosis, urate uropathy and hyperoxaluria are autosomal recessive conditions.
  - the most common cause being increased gastrointestinal (GI) absorption of calcium.
  - The most common stones are calcium oxalate stones.
- there appears to be a male predominance with a 2:1 ratio.

### Risk factors for oxalate stones (Calcium oxalate).

- foods high in oxalate, (such as spinach, rhubarb and tea)
  - In patients who have oxalate kidney stones, dietary restrictions are necessary. Foods that should be avoided include: spinach, nuts, chocolate, dry beans, rhubarb and strawberries.
- calcium-restricted diet
- **gastrointestinal disease such as Crohn's which increase colonic oxalate absorption**
  - in malabsorption, the calcium in the small bowel is bound by the unabsorbed excess fatty acids. Oxalates are left free and are excessively absorbed. Subsequently, they can deposit in the kidney to form stones.
- enteric oxaluria may occur in a number of disorders in which **malabsorption results in excessive colonic absorption of oxalate**. These include:
  - ⇒ Coeliac disease
  - ⇒ **Crohn's disease**
  - ⇒ Chronic pancreatitis, and

- ⇒ **Short bowel syndrome.**
  - Bile salts in the colon increase oxalate absorption.
- **Excess vitamin C can be converted to oxalic acid in the body. Subsequent hyperoxaluria can lead to the formation of a kidney stone.**

### Primary hyperoxaluria

- inherited enzyme deficiency that leads to excessive metabolism of oxalate.
- There are three types:
  - ⇒ types I and III are due to an enzyme defect in the liver glyoxalate pathway
  - ⇒ Type I is the commonest and results in widespread calcium oxalate deposition throughout the body.
  - ⇒ in type II there is failure of reduction of glyoxalate to glycolate.
- Treatment is aimed at increasing urinary pH to make calcium oxalate more soluble. This is by administering supplemental citrate and magnesium.
- Renal insufficiency is common, and patients require a combined liver and kidney transplant in type I disease.

### Risk factors for urate stones

- gout
- ileostomy:
  - ⇒ loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid
- high purine intake,
- High cell turnover. (for example, haematological malignancy).
  - ⇒ Primary polycythaemia would predispose to uric acid stone formation, whereas secondary polycythaemia does not.
- Dehydration
- **Thiazide diuretics → cause hyperuricaemia and can predispose to hyperuricosuria and uric acid stone formation.**

### Stag-horn calculi (Triple phosphate stones: magnesium ammonium phosphate):

- involve the renal pelvis and extend into at least 2 calyces.
- They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate).
- Urea plasma urea lyticum and Proteus infections predispose to their formation
  - ⇒ Proteus produces urease, which leads to hydrolysis of urea to produce ammonia, this leads to precipitation of organic and inorganic salts, one of which is known as struvite, or magnesium ammonium phosphate
- **classically produced by urea splitting organisms such as Klebsiella or Proteus.**

### Drug causes

- drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- **topiramate (anti-epileptic) increase the propensity to form calcium phosphate stones.**
- thiazides can prevent calcium stones (increase distal tubular calcium resorption)

### Renal conditions associated with recurrent urinary tract infections:

- **Reflux nephropathy.**
- Renal stone (but is less likely than reflux nephropathy)

### Hypercalcuria

Thiazide diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation.

- high urine calcium that is not due to hypercalcemia (idiopathic hypercalciuria)
- Idiopathic hypercalciuria is often familial, the most common cause being increased gastrointestinal absorption of calcium.
- predisposes to stone formation.
- The 24-hour urine is an essential component of the initial evaluation and guides recommendations for prevention
- Treatment** including dietary calcium restriction and pharmacological management.
- Both thiazide diuretics and potassium citrate can be used to reduce urinary excretion of calcium. **Potassium citrate is generally preferred as it has fewer side effects**, and is therefore better tolerated.
- Thiazide diuretics are the drug treatment of choice as they act directly on the renal tubule to reduce urinary calcium excretion** (there is a disagreement between onexamination and pastest in which drug is better for hypercalciuria? But after thorough review of sources and update, **thiazide is a better choice than potassium citrate**)
- Dietary calcium restriction alone has minimal effect on calciuria, given the large amount of calcium that can be mobilised from bone..
- Loop diuretics increase urinary excretion of calcium, and therefore would exacerbate calcium renal stone formation.
- Pencillamine is used in the management of hypercalciuria associated with Wilson's disease
- Idiopathic hypercalciuria** has a familial or sporadic pattern. In the familial pattern an **autosomal dominant inheritance** is present. The type of the disease is identical in affected members of the same family and **the typical presentation is of recurrent urinary calculi**.

### Imaging

The table below summarises the appearance of different types of renal stone on x-ray

Type	Frequency	Radiograph appearance
Calcium oxalate <b>(the most common)</b>	40%	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Triple phosphate stones	10%	Opaque
Calcium phosphate	10%	Opaque
Urate stones	5-10%	Radio-lucent
Cystine stones	1%	Semi-opaque, 'ground-glass' appearance
Xanthine stones	<1%	Radio-lucent

- patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- the imaging of choice is a non-contrast CT (NCCT). 99% of stones are identifiable on NCCT.

**Imaging** (European Association of Urology guidelines 2016)

- Ultrasound (US) should be used as the primary diagnostic imaging tool.
  - ⇒ US is safe (no risk of radiation), reproducible and inexpensive.
  - ⇒ US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones.
  - ⇒ the preferred method of imaging in pregnant women.
- KUB (kidney-ureter-bladder radiography) x-ray
  - ⇒ The sensitivity: 44-77% and specificity: 80-87%.
  - ⇒ should not be performed if NCCT is considered.
  - ⇒ KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up.
- Non-contrast CT (NCCT) (Non-contrast helical CT kidneys, ureters and bladder (**CT KUB**))
  - ⇒ **The imaging of choice** is a non-contrast CT (NCCT).
  - ⇒ become **the standard** for diagnosing acute flank pain
  - ⇒ 99% of stones are identifiable on NCCT.
  - ⇒ Following initial ultrasound assessment, use non-contrast-CT to confirm stone
  - ⇒ more accurate than intravenous urography (IVU), so has replaced it.
- **Imaging in pregnant women**
  - first-line → ultrasound as the preferred method of imaging
  - second-line → magnetic resonance imaging (MRI)
  - last-line option → low-dose computed tomography (CT)

**Management****Acute management of renal colic****Medication**

- the British Association of Urological Surgeons (BAUS) recommend diclofenac (intramuscular/oral) as the analgesia of choice for renal colic\*
  - ⇒ \*Diclofenac use is now less common following the MHRA warnings' about cardiovascular risk.
  - ⇒ It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen
- BAUS also endorse the widespread use of alpha-adrenergic blockers to aid ureteric stone passage
- Stones < 5 mm will usually pass spontaneously.
- Lithotripsy and nephrolithotomy may be for severe cases.

**Prevention of renal stones**

**Calcium stones** may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- high fluid intake
  - ⇒ **the main initial treatment**
  - ⇒ should aim for a daily urinary output in excess of 2000 ml.
- low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- **thiazides diuretics (increase distal tubular calcium resorption)** and hence lower calcium concentration in the urine.

**Oxalate stones**

- cholestyramine reduces urinary oxalate secretion
- pyridoxine reduces urinary oxalate secretion
- **High fluid intake and calcium carbonate are mainstay of prevention.**

- Avoid foods high in oxalate such as chocolate, rhubarb and nuts .
- Increasing dietary calcium intake decreases urinary oxalate excretion by reducing absorption (as free oxalate is bound).
- **Other treatments which can help enteric hyperoxaluria include:**
  - ⇒ Calcium, cholestyramine and magnesium - bind strongly to free intestinal oxalate, preventing absorption.
  - ⇒ Iron and aluminium - act as intestinal oxalate binding agents.
  - ⇒ Potassium citrate - alkalinises the urine, which reduces urinary oxalate excretion.
    - propensity to form stones is reduced when citrate intake is increased.

### **Uric acid stones**

- allopurinol
- urinary alkalinization e.g. oral bicarbonate
- Reducing intake of offal is most helpful at reducing urate excretion

### **Contraindications to lithotripsy**

- **absolute contraindication → uncorrected bleeding disorder**
- relative contraindications → Ureteric stricture, UTI and cardiac pacemaker

**MRCPUK-part-1-September 2008 exam: What is the most likely composition of a stag-horn calculus? Struvite**

**MRCPUK-part-1-September 2012 exam: What are stag-horn calculi normally composed of? Magnesium ammonium phosphate**

## **Cystinuria**

- The commonest inborn error of amino acid transport.
- **Amino acids excreted in urine are cystine, ornithine, arginine and lysine (mnemonic - COAL).**
- The glomerulus is unable to resorb these amino acids, and they are therefore excreted into the urine.

### **Genetics**

- **autosomal recessive** condition.
- The rBAT gene is responsible,
- There are two genes identified:
  - ⇒ SLC3A1 (Chromosome 2)and
  - ⇒ SLC7A9(Chromosome 19)

### **Features:**

- Cystinuria usually presents with **recurrent nephrolithiasis** in the form of cystine stones (which are often bilateral, multiple, and can form staghorns).
- The renal stones are semi radio-opaque due to the presence of sulphur. (Semi-opaque, 'ground-glass' appearance)
  - ⇒ On plain film, which is not used as much in the UK any more, they are radio-lucent.
  - ⇒ On CT, as with almost all stones, cysteine stones are radio-opaque.

**Diagnosis**

- Diagnosis of cystinuria can be made by **stone analysis**; such stones are pale yellow, and analysis reveals high cystine levels. It can then be confirmed by an amino acid chromatogram and quantification of cystine excretion.
- cystine may precipitate out as **pathognomonic hexagonally-shaped crystals**

**Management** includes:

- conservative
  - high fluid intake (>4 L/day);
  - alkalinisation
  - Urine pH should be regularly monitored (aiming for 7.5-8), with sodium bicarbonate being used if necessary (not in hypertensive patients or those with renal failure).
  - The aim of such treatment is to reduce the urinary cystine concentration to below 300 mg/L.
- If this fails, d-penicillamine, alpha-mercaptopropionylglycine or captopril can be used.
- Cystine stones are not easily broken by lithotripsy, and therefore percutaneous removal is most often used.

**Cystinosis**

- autosomal recessive
- caused by mutations in the CTNS gene, which encodes a lysosomal transporter of the amino acid cystine. Without this transporter, cystine accumulates in the lysosomes of proximal tubule cells, eventually leading to cell toxicity.
- **the most common form of Fanconi syndrome in children.**
- occurs almost exclusively in **whites**.

**Feature**

- presents in the first year of life with:
  - failure to thrive, and rickets
  - progressive renal damage (Renal failure develops before the age of 10 years)
  - polyuria, polydipsia
  - Visual impairment (occurs as a result of cystine deposits in the retina and cornea)
  - hypothyroidism

## Renal tubular acidosis (RTA)

Recurrent kidney stones, hypokalaemia, acidosis and a normal anion gap is a typical presentation for RTA type 1.

RTA type 2 present with similar biochemical features but is more unlikely to have a history of kidney stones.

Treatment of RTA involves correction of the acidaemia with oral sodium bicarbonate, sodium citrate or potassium citrate

- All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

### Type 1 RTA (distal) (acid retention)

- Inability to generate acid urine (secrete H<sup>+</sup>) by a failure of the alpha intercalated cells of the distal tubule to excrete hydrogen ions.
- Causes
  - Idiopathic, gene defects,
  - Autoimmune diseases such as primary biliary cirrhosis, thyroiditis RA, SLE, Sjogren's,
  - Drugs: **amphotericin B toxicity**, analgesic nephropathy ,
  - hypergammaglobulinaemic states,
- Features
  - hypokalaemia, (as K<sup>+</sup> reabsorption is linked to H<sup>+</sup> excretion).
  - acidosis
  - low urinary ammonium production
  - inability to lower the urinary pH below 5.3 after ammonium chloride administration despite systemic acidosis
  - low urinary citrate
  - **Hypercalciuria:** These predispose to renal stones, rickets or osteomalacia and nephrocalcinosis
- Complications
  - **nephrocalcinosis and renal stones** ( Alkaline urine increases the risk of calcium deposition)
  - **Osteomalacia** develops because of calcium loss and buffering of retained H<sup>+</sup> in bone
- Management
  - Bicarbonate and potassium supplements should be given to maintain adequate plasma levels.



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

### Type 2 RTA (proximal) (bicarbonate loss)

**Fanconi syndrome (RTA type 2) is associated with Wilson's disease**

- decreased HCO<sub>3</sub>- reabsorption in proximal tubule
- very rare in adult practice
- As the distal tubule functions normally, the acidosis is less severe than type 1 RTA, and they urine has a pH of less than 5.3.
- **Causes include**
  - idiopathic,
  - as part of Fanconi syndrome,
  - **Wilson's disease**,
  - cystinosis,
  - lead poisoning
  - myeloma
  - outdated tetracyclines
  - carbonic anhydrase inhibitors
- **Features**
  - acidosis, hypokalaemia
  - **hypophosphataemia** → increased risk for hypophosphatemic rickets.
- **Complications**
  - osteomalacia (Phosphate wasting results in marked bone demineralisation)

### Type 4 RTA (hyperkalaemic)( hypoaldosteronism)

- the most common renal tubular disorders
- **Causes include:**
  - **Aldosterone deficiency (hypoaldosteronism):** decreased aldosterone production, secondary to:
    - adrenal insufficiency
    - **diabetes**

- ❖ Diabetic nephropathy → decreased renin production → **Hyporeninaemic hypoaldosteronism** → **low sodium and raised potassium**
- ❖ Patients with diabetes may have impaired extrarenal potassium homeostasis, caused by a lack of insulin, and autonomic neuropathy with resulting impaired beta<sub>2</sub>-mediated influx of potassium into cells.
- chronic reflux nephropathy
- **Aldosterone resistance**
  - → 1. Drugs:
    - ❖ **Non-steroidal anti-inflammatories,**
    - ❖ angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers,
    - ❖ eplerenone, spironolactone,
    - ❖ trimethoprim,
    - ❖ pentamidine
    - ❖ heparin,
    - ❖ cyclosporine
  - → 2. Pseudohypoaldosteronism
- **Features:**
  - **hyperkalaemia**
    - usually mild but may be exacerbated by drugs such as beta-blockers and ACE inhibitors.
  - **low sodium**
  - metabolic acidosis
  - Urinary pH is commonly normal
  - reduction in renin and aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- **Treatment:**
  - ⇒ Treatment is usually successful with **conservative measures** such as:
    - stopping provocative agents,
    - low potassium diet.
  - ⇒ Small doses of **fludrocortisone** could be considered for refractory cases.

### **Type 3 RTA** (Juvenile RTA) is combined proximal & distal RTA.

- autosomal recessive
- Results from inherited carbonic anhydrase II deficiency.
- 70% of the reported cases are from the Magreb region of North Africa
- rarely discussed
- described as a failure to generate NH<sub>3</sub> in the setting of a decreased glomerular filtration rate,
- **Features:**
  - normokalaemic hyperchloraemic metabolic acidosis.
  - A syndrome of osteopetrosis
  - Renal tubular acidosis
  - Cerebral calcification
  - Mental retardation.

Type	Type 1	Type 2	Type 4
<b>Location</b>	Distal tubules	Proximal tubules	Adrenal
<b>Acidosis?</b>	Yes (severe)	Yes	Mild when present
<b>Potassium</b>	Hypokalemia	Hypokalemia	Hyperkalemia
<b>Pathophysiology</b>	H <sup>+</sup> secretion	Bicarb reabsorption	hypoaldosteronism/ pseudohypoaldosteronism

**January 2010 exam:** Which feature is most likely to be seen as a consequence of type 1 renal tubular acidosis?

→ **Nephrocalcinosis**

### Renal vascular disease (RAS)

Flash pulmonary oedema, U&Es worse on ACE inhibitor,  
asymmetrical kidneys → renal artery stenosis - do MR angiography

The presence of difficult to treat hypertension, renal impairment, evidence of other atherosclerotic disease (carotid bruit) and discrepant renal size makes **renovascular disease a distinct possibility.**

- Renovascular disease is due to disease affecting the arterial supply of the kidney(s).
- The resulting renal hypoperfusion leads to hyperactivation of the renin-angiotensin-aldosterone axis, causing hypertension.
- In one third of cases the disease is bilateral; 40% may have peripheral vascular disease and there may be proteinuria.

#### Suspicion for renal artery stenosis:

- Current UK guidelines with regard to chronic kidney disease recommend **referral for further investigation of atherosclerotic renal artery stenosis** when there is:
  - Refractory hypertension (BP >150/90 mmHg despite 3 antihypertensives);
  - Recurrent episodes of pulmonary oedema despite normal left ventricular function;
  - **Rise of >20% serum creatinine or fall of GFR >15% over 12 months** with high clinical suspicion of widespread atherosclerosis, **or during the first 2 months after initiation with an ACE inhibitor or angiotensin receptor blocker.**

A rise in serum creatinine **more than 20% above the baseline** after starting an (ACEI) → hold the drug, monitor renal function and investigate for renal artery stenosis.

**Unilateral renal artery stenosis (RAS)** has two common causes:

1. **Atherosclerosis:** usually men over the age of 45 years and typically involves the aortic orifice or the proximal 2 cm of the main renal artery.
2. **Fibromuscular dysplasia:** usually women younger than the age of 50 years and typically involves the middle and distal main renal artery or the intrarenal branches.

### Causes

- Atherosclerosis is most common cause (> 95% of patients).
- Arteriosclerosis (renal artery sclerosis) is a more common cause of RAS than fibromuscular dysplasia.
  - ⇒ 40% may have peripheral vascular disease (PWD) with intermittent claudication
  - ⇒ there may be proteinuria.
- In younger patients however, fibromuscular dysplasia (FMD) needs to be considered.
  - FMD is more common in young women
  - and characteristically has a 'string of beads' appearance on angiography.
  - Patients respond well to balloon angioplasty
  - renal artery narrowing is unlikely to progress
- Takayasu's arteritis
- Congenital RAS is extremely rare and may be associated with coarctation of the aorta

### Associated risk factors

- Smoking and hypertension that cause atheroma elsewhere in the body.

### Presentation

It may present as:

- Hypertension, which can be resistant to standard treatment.
- chronic renal failure
- 'flash' pulmonary oedema.
- It can also lead to renal impairment when patients are started on ACE inhibitors or angiotensin-II receptor antagonists, hypokalaemia or flash pulmonary oedema.
  - ACE inhibitor → reduce vasoconstriction in the **efferent** arterioles, which in turn reduces glomerular filtration pressure. In patients with RAS this can often prompt a precipitous drop in glomerular filtration rate.
  - A rise in creatinine of 15% from baseline is expected with commencement of an ACE-inhibitor.

### Investigation

- **MR angiography**
  - the investigation of choice and can be performed safely in patients with CKD stage 3 and 4
- CT angiography.
  - Commonly used but can be complicated by radio-contrast nephropathy in patients with CKD.
- conventional renal angiography
  - less commonly performed used nowadays, but may still have a role when planning surgery
- U/S

- Atherosclerotic renal artery stenosis (RAS) is suggested by the asymmetric reduction in renal size on U/S, with mild proteinuria quite common in the condition.
- Typical ultrasound changes are asymmetrical kidneys; the affected kidney >2 cm smaller than the unaffected kidney.
- ↑↑ Aldosterone
- ↑↑ Renin
  - Serum renin can differentiate renal artery stenosis ( $\uparrow\uparrow$  Renin + $\uparrow\uparrow$  Aldosterone) from primary hyperaldosteronism ( $\downarrow\downarrow$  Renin + $\uparrow\uparrow$  Aldosterone)
  - ↑↑ Renin work as a mechanism to improve renal perfusion.
  - ↓↓ Renin in primary hyperaldosteronism is due to the resulting hypertension causing excessive renal perfusion, which results in decreased renin production (negative feedback mechanism).

**Flash pulmonary edema, U&Es worse on ACE inhibitor,  
asymmetrical kidneys**



#### Treatment:

- Optimize vascular risk factors,
- cautious use of ACE inhibitors and angiotensin-II receptor antagonists and avoiding other nephrotoxics.
- The current evidence favours medical therapy in these patients, that is, an antiplatelet agent (aspirin), lipid lowering therapy (simvastatin) and tight blood pressure control (amlodipine).
- No benefit of vascular intervention such as stenting.
  - The ASTRAL trial showed no significant difference between stenting and medical therapy, it is often decided on an individual level.
- Although patients with unilateral renal artery stenosis who have recurrent pulmonary oedema may benefit from stenting, the optimal first step is control of hypertension. Per se, better targeting of blood pressure is likely to reduce the number of episodes of heart failure.
- Renal artery stenting to reduce further risk of pulmonary oedema is the next step following medical therapy to control blood pressure. The subsequent reduction in renin production will reduce the incidence of heart failure.
- Although surgical renal artery bypass is successful, it is invasive and associated with significant operative morbidity versus percutaneous stent insertion.

Indication for stenting in renal artery stenosis:(mrcpass.com)

- hemodynamically significant renal artery stenosis
  - Flash pulmonary oedema
  - episodic pulmonary edema,
  - congestive cardiac failure,
  - unstable angina.

#### Prognosis

- poor prognosis (80% mortality at five years) is related to concurrent coronary disease.

## Lupus nephritis (SLE: renal complications)

### Epidemiology

- Lupus nephritis affects a **third of patients** early in the disease
- it is frequently un-recognised until nephritic and/or nephrotic syndrome with renal failure occur.

### WHO classification

- class I: normal kidney
- class II: mesangial glomerulonephritis
- class III: focal (and segmental) proliferative glomerulonephritis
- **class IV: diffuse proliferative glomerulonephritis**
- class V: diffuse membranous glomerulonephritis
- **class VI: sclerosing glomerulonephritis**
  - **end stage renal disease**
  - **irreversible**
  - **not respond to any immunosuppression**

### Class IV (diffuse proliferative glomerulonephritis)

- the most common type in SLE.
- **the most severe form**, affecting > 50% of glomeruli,
  - carries the **worst prognosis** for progression to renal failure
- **Renal biopsy** characteristically shows:
  - endothelial and mesangial proliferation, '**wire-loop**' appearance
  - the capillary wall may be thickened secondary to immune complex deposition
    - electron microscopy shows subendothelial immune complex deposits
  - **granular appearance on immunofluorescence**
- **Treatment**
  - **high dose steroids and pulses of intravenous cyclophosphamide** (initially given monthly for six months and then quarterly).
    - Pulsed intravenous cyclophosphamide appears to be as effective as oral cyclophosphamide but has lower toxicity.

### Class V (Membranous nephropathy in SLE)

- **Nephrotic syndrome without haematuria in a patient with (SLE) suggests membranous nephropathy (class V)**
- **The lesion is differentiated from idiopathic (non-lupus) membranous nephropathy by:**
  - The presence of tubulo-reticular structures on electron microscopy, immune deposits along the tubular basement membrane (in addition to the glomerular basement membrane)
  - and the presence of concurrent subendothelial and mesangial immune deposits (in addition to the subepithelial deposits typical of membranous)
  - Class V lupus nephritis is the only form of renal disease in SLE where serological and clinical manifestations of the underlying disease may be absent. Complement levels may be normal and dsDNA antibodies may be absent

### Clinical features

- Hypertension is found at presentation in 20-50%
- 20-30% present with acute renal failure
- **Lupus nephritis typically occurs in SLE patients with extrarenal symptoms such as a rash, arthralgia, Raynaud's phenomenon, and pleuro-pericarditis**

**Laboratory features**

- Proteinuria is found in all patients with lupus nephritis and in 50-60% of cases is heavy enough to lead to a nephrotic syndrome
- Microscopic haematuria (80% of patients)
- In lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function , for histological classification ,disease activity, chronicity and prognosis.

**Immunological features**

- the pathognomonic feature of lupus on renal biopsy is 'full house' immunology on immunostaining, ie **mesangial deposition of IgA, IgG, IgM, C3 and C4**
  - This differentiates the necrotising glomerulonephritis with crescent formation seen in lupus from a similar pattern which is seen in systemic vasculitis, as the latter condition is 'pauci immune', ie no immunoglobulin deposition
- Lupus nephritis is associated with **activation of the classical pathway**, and often associated with **suppression of both C3 and C4**.

**Prognosis**

- **Features associated with a poorer prognosis**, and increased risk of progression to end stage renal failure include:
  - young age (<23)
  - Increased serum creatinine
  - Diffuse proliferative lesions (WHO classification class IV) and
  - high chronicity index on renal histologic analysis.

**Management**

- treat hypertension
- corticosteroids if clinical evidence of disease
- immunosuppressants e.g. azathioprine/cyclophosphamide
- patients with type IV (and sometimes type III, where < 50% of glomeruli are involved) should be treated with a combination of cyclophosphamide and steroids.

**Urinary incontinence (UI)****Epidemiology**

- common problem, affect around 4-5% of the population.
- more common in elderly females.

**Risk factors**

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

**Classification**

- **urge** incontinence /overactive bladder (OAB):
  - due to detrusor over activity
  - characterized by involuntary loss of urine after sudden desire to urinate.
  - Cystourethroscopy may be performed in patients with urge incontinence to exclude the presence of stones as the primary cause.
  - Urge incontinence may present with frequency, which is defined as urinating more than eight times in the 24 hours.
- **stress** incontinence: leaking small amounts when coughing or laughing
  - coughing, sneezing, and laughing → ↑ intra-abdominal pressure and overwhelm the strength of bladder sphincter muscles in those with weak pelvic floors.

- Outlet incompetence in stress incontinence is due to:
  - urethral hypermobility or
  - intrinsic sphincteric deficiency.
- most common in younger women.
- There is an increased risk of stress incontinence with pregnancy
- Obesity → ↑ pressure on pelvic tissues → weakening of pelvic structures.
- **mixed incontinence:** both urge and stress
- **overflow incontinence:**
  - causes
    - bladder outlet obstruction, e.g. prostate enlargement
    - Neurogenic bladder (detrusor areflexia)
      - characterized by:
        - ❖ absent bladder sensation, decreased tone, increased capacity, hesitancy, and significant residual urine.
      - ❖ caused by :
        - ➔ diabetes mellitus,
        - ➔ **multiple sclerosis**,
        - ➔ cerebrovascular disease (Upper motor neuron lesions) → affect descending pathways from the brain → delayed bladder sensation → urinary retention → overflow incontinence.
        - ➔ **Parkinson's disease**,
        - ➔ spinal injuries (damage to the conus, cauda equina, and sometimes S2-4 nerve roots)
  - diagnosis
    - **Cystometry is the gold standard for the diagnosis**
    - increased post-void residual urine on catheterization or ultrasound.
  - Treatment
    - relieve obstruction e.g. catheterization
    - Sacral nerve stimulation can be used for the management of patients with **idiopathic detrusor inactivity**

### Investigation

- **bladder diaries** should be completed for a minimum of 3 days
- vaginal examination to exclude cystocele
- urine dipstick and culture
- urodynamic studies

**Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative**

**antimuscarinics (e.g. Oxybutynin, Tolterodine ) the usual treatment for urge incontinence are contraindicated in patients with a history of urinary retention.**

**Management** depends on whether urge or stress UI is the predominant picture.

- If **urge incontinence is predominant:**
  - bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
  - bladder stabilising drugs: (antimuscarinic) is first-line
    - modern anticholinergics (**Solifenacin**) are recommended vs traditional agents, such as oxybutynin:

- ❖ because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly.
- A meta-analysis has shown that the class as a whole may affect the long-term risk of dementia. As such, dose titration to the minimum level required to control symptoms is recommended.
- **Oxybutynin** is an effective treatment for detrusor instability and is a parasympathetic muscarinic antagonist.
  - ❖ **dry mouth is a problem in up to 70% of cases.**
  - ❖ not recommended for elderly because it is the most negative of the anticholinergic class with respect to its effects on cognitive function.
- In older men, **Tolterodine** is preferred to oxybutynin as the latter has a greater risk of causing confusion.
- If anticholinergics fail or are contraindicated, mirabegron may be trialled.
  - ❖ **Mirabegron activates the  $\beta_3$  adrenergic receptor** in the detrusor muscle in the bladder, which leads to muscle relaxation and an increase in bladder capacity
- surgical management: e.g. **sacral nerve stimulation**
  - indicated if **not respond** to pharmacological intervention or **unable to tolerate it**.
- If **stress incontinence** is predominant:
  - pelvic floor muscle training:
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
  - surgical procedures: e.g. retropubic mid-urethral tape procedures

**Which pharmacotherapies represents the most appropriate initial management step for overactive bladder?**

→ **Tolterodine**

**MRCPUK-part-2-March 2017:** A 72-year-old woman with urinary incontinence. Urodynamic studies confirm detrusor overactivity and significant post-voiding residual volume. She is unable to tolerate oxybutynin for bladder control due to postural hypotension and GI symptoms. what is the most appropriate intervention for control of her bladder symptoms?

→ **Sacral nerve stimulator**

**MRCPUK-part-2-March 2018:** A 74-year-old woman with urge incontinence. Urine dipstick testing and post-void residual bladder volume are normal. Routine urea and electrolytes are also normal. She has attempted bladder training exercises but has not managed to improve her symptoms.

**What is the most appropriate next step?**

→ **Solifenacin**

- modern anticholinergics (**Solifenacin**) are recommended vs traditional agents, such as oxybutynin, because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly.

## Urinary retention

- **Drug causes**
  - Amitriptyline has anticholinergic effects being associated with tachycardia, dry mouth and urinary retention.
  - These features are not typical of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine with urinary retention and dry mouth rarely reported.
  - Diazepam, a benzodiazepine does not have anticholinergic effects. It has been associated with urinary retention, but this is much less common than with anticholinergics.
- **Complication of recovery from obstructive uropathy:**
  - Amelioration of urinary obstruction and subsequent recovery initially results in a large electrolyte and water loss. And over the next few days as the tubules recover their function his urine will begin to concentrate appropriately.
  - The main approach to management in such patients is to ensure they remain adequately hydrated while their kidneys recover their ability to concentrate urine and manage fluid balance.
    - Supplement oral intake with intravenous fluids
  - The patient should not be fluid restricted as this would lead to severe dehydration.
  - Osmotic cerebral changes precipitated by urinary sodium loss, the major intravascular cation, is the cause of drowsiness.
  - Hypocalcaemia and hypomagnesaemia may occur as tubular reabsorption is suboptimal in the early stages of recovery but is unlikely to affect conscious level.
  - Acid-base status should improve after relief of the obstruction.

## Benign prostatic hypertrophy (BPH)

### Risk factors

- Age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH
- Ethnicity: Black > White > Asian

### Features

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorized into:

- Voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying
- Storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia
- Post-micturition: dribbling
- Complications: urinary tract infection, retention, obstructive uropathy

### Investigations

- If the suspicion is of prostatic hypertrophy, then **post-void residual volume is the best way to estimate the degree of bladder obstruction.**

### Management options

- Watchful waiting
- Medication:

- **$\alpha$ -blocker (e.g. tamsulosin, alfuzosin) → for rapid symptom relief**
  - Considered first-line, improve symptoms in around 70% of men
  - **$\alpha$ -Blockers relax the smooth muscle of the bladder neck and can improve urinary flow rates**
  - ↓ smooth muscle tone (prostate and bladder)
  - Adverse effects: dizziness, postural hypotension, dry mouth, depression
- **5  $\alpha$ -reductase inhibitors (e.g. finasteride and dutasteride) → to reduce prostate volume**
  - Block the conversion of testosterone to dihydrotestosterone (DHT), which induces BPH
  - Unlike  $\alpha$ -1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months.
  - They may also ↓ PSA concentrations by up to 50%
  - Adverse effects: erectile dysfunction, ↓ libido, ejaculation problems, gynecomastia
- The use of **combination** ( $\alpha$ -1 antagonists, 5  $\alpha$ -reductase inhibitors) therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial
- Surgery: transurethral resection of prostate (TURP)

**Medications for BPH**

	$\alpha_1$ -BLOCKERS	$5\alpha$ -REDUCTASE INHIBITORS
Drugs	Prazosin, doxazosin, terazosin, tamsulosin.	Finasteride.
Mechanism	↓ contractility of the prostate and bladder neck.	Block testosterone conversion to the more potent dihydrotestosterone.
Results	Improve symptoms and urinary flow rates; more effective than 5 $\alpha$ -reductase inhibitors for symptom relief.	Improve symptoms; ↓ prostate size and PSA, especially in men with larger prostates.
Side effects	<b>Orthostatic hypotension</b> , nasal congestion, dizziness, fatigue.	↓ libido, ejaculatory dysfunction, impotence.

## Prostatic carcinoma

A man of advanced age presenting with bony metastases is most likely to have **metastatic prostate cancer**.

### Overview

- These are **adenocarcinomas**
- hormonal factors are thought to play a part in the aetiology
- As a rule, prostate cancer is more aggressive in younger men.
- Prostate cancer begins in the outer peripheral zone of the prostate, and grows *outward*, invading surrounding tissue. BPH begins in an area of the inner prostate called the transition zone, a ring of tissue that makes a natural circle around the urethra. In BPH, the growth is *inward* toward the prostate's core.

### Epidemiology

- Prostate cancer is now the most common cancer in adult males in the UK and is the second most common cause of death due to cancer in men after lung cancer.
- **By 80 years of age some 80% of men appear to have malignant foci within the prostate gland**
- Prostatic carcinoma is found in 10-30% of patients with BPH.

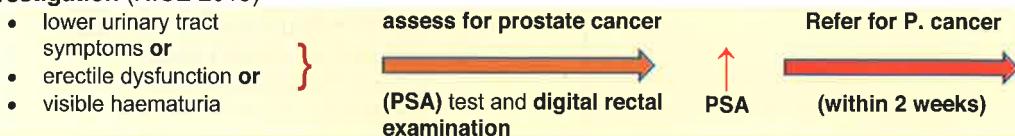
### Risk factors (BPH is not a risk factor)

- ↑ age (the strongest risk)
- obesity
- High intake of animal fats
- low intake of selenium
- Afro-Caribbean ethnicity
- family history: 5-10% of cases have a strong family history

### Features

- Localised prostate cancer is often asymptomatic. This is partly because cancers tend to develop in the periphery of the prostate and hence don't cause obstructive symptoms early on.
- bladder outlet obstruction: hesitancy, urinary retention
- haematuria, haematospermia
- pain: back, perineal or testicular
- digital rectal examination: asymmetrical, hard, nodular enlargement with loss of median sulcus

### Investigation (NICE 2015)



- Prostate-specific antigen (PSA)
  - (PSA) may be elevated in:
    - Prostatitis
    - Benign prostatic hyperplasia, and
    - Prostate cancer.
  - Some prostatic carcinomas may not be associated with an elevated PSA.
  - **False positives PSA associated with:**
    - UTI & catheterisation thus should be measured at least two weeks after a treated UTI.
    - prostatic needle biopsy
    - PR examination
  - **False negatives PSA:** Finasteride is the only factor likely to decrease the level of serum PSA.
- **Trans-rectal prostatic biopsy**
  - The most commonly used pathological grading system is the **Gleason score**
  - The most well differentiated tumours have a Gleason score of 2, and the most poorly differentiated a Gleason score of 10.
- Bone scan, CT abdomen and pelvis also indicated to assess both extent of bony metastases and local spread. (metastases may mimic the appearance of Paget's)

**Management:** depends on histological grading of the tumour

prostate cancer stage	Treatment options
<b>Localised (T1/T2)</b> T1 - clinically unapparent disease T2 - palpable disease confined to prostate	<ul style="list-style-type: none"> <li>conservative: active monitoring &amp; watchful waiting</li> <li>radical prostatectomy</li> <li>radiotherapy: external beam and brachytherapy</li> </ul>
<b>Localised advanced (T3/T4)</b> T3 = beyond prostatic capsule T4 = involves bladder neck or rectum Most men will have occult mets	<ul style="list-style-type: none"> <li>hormonal therapy: see below</li> <li>radical prostatectomy</li> <li>radiotherapy: external beam and brachytherapy</li> </ul>
<b>Metastatic</b>	<p><b>hormonal therapy</b></p> <ul style="list-style-type: none"> <li>Synthetic GnRH agonist           <ul style="list-style-type: none"> <li>e.g. Goserelin (Zoladex) and <b>Leuprolide</b></li> <li>cover initially with anti-androgen to prevent rise in testosterone</li> </ul> </li> <li>Anti-androgen           <ul style="list-style-type: none"> <li>such as bicalutamide, or <b>flutamide</b></li> <li>cyproterone acetate prevents DHT binding from intracytoplasmic protein complexes</li> </ul> </li> </ul> <p><b>Orchiectomy</b></p>

- Synthetic GnRH agonist (Buserelin, Goserelin, **leuprolide**)**
  - Decreased androgen production**
  - gonadotrophin releasing hormone agonist that exerts its actions at the level of the pituitary gland.
  - Initially treatment causes increased gonadotrophin release; however, after a few weeks of continued therapy, gonadotrophin production is inhibited, and testosterone levels fall.
  - The initial increase in testosterone levels may be accompanied by a 'flare' in disease symptoms in some patients.
- docetaxel-based chemotherapy**
  - indicated only for patients with hormone-refractory cancer.
- Samarium-153 is a radionuclide** useful in treating prostate cancer with painful bone metastases and is not useful when the patient is asymptomatic.

**What histological grading system is used to grade prostate cancer?**

➤ **Gleason grading**

- Gleason grading takes account of the most prevalent tumour pattern in the pathological system (1-5) and the second most prevalent tumour pattern (1-5).
- It is presented as, for example, Gleason 3+4 = 7. This is important as a Gleason 4+3 = 7 obviously has a worse prognosis than a Gleason 3+4 = 7 even though they both have the same total score.

## Renal cell cancer (RCC) (also known as hypernephroma)

### **Classical triad: haematuria, loin pain, abdominal mass**

#### **Overview**

- usually arise from the epithelial cells of the proximal convoluted tubule.
- Clear cell RCC is the most common histological variant (~ 80% of all cases).
- Most cases are sporadic, although positive family history increases risk 4-fold.

## Epidemiology

- Most common malignancy of the renal parenchyma (85% of renal cancers in adults are RCC)
- Sex: ♂ > ♀ (~ 2:1)
- Age of onset: 60–80 years

## Associations

- smoking
- von Hippel-Lindau syndrome (**the most likely inherited condition**)
  - is an inherited syndrome in which cysts or tumours in the kidney, pancreas, adrenal gland, epididymis, cerebellum, and spinal cord may form.
  - (30 - 50% develops renal cell tumors)
- tuberous sclerosis
- incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease

## Features

- Often asymptomatic and diagnosed incidentally.
- the classical triad of: Haematuria, Loin pain, A palpable mass.
  - only 5–10% of patients present with all three components of the triad
  - Haematuria is the most common presenting symptom (50-60% of cases)
- Anaemia (common) → Fatigue
- **Symptoms of local spread**
  - left varicocele (due to occlusion of left testicular vein)
  - Budd-Chiari syndrome: (due to hepatic vein obstruction → hepatomegaly, ascites, lower limb edema, hepatic dysfunction)
- Paraneoplastic syndromes:
  - may secrete renin → Hypertension
  - may secrete erythropoietin (polycythaemia) → Increased plasma viscosity.
  - may secrete parathyroid hormone (hypercalcaemia),
  - may secrete ACTH → Secondary hypercortisolism → myopathy
- Symptoms of metastatic disease
  - 25% have metastases at presentation
  - **Commonest sites of metastases are lung (50-60%) and bone (30-40%)**
- pyrexia of unknown origin
- Urinalysis may show sterile pyuria

## Investigations

- **Ultrasound scan of the renal tract**
  - **the first investigation of choice**,
    - as it is able to pick up 95% of renal cell carcinomas greater than 1 cm in diameter.
    - It would also exclude infective or inflammatory collections within the renal tract.
- CT abdomen/pelvis (contrast-enhanced CT)
  - **Definitive** test for diagnosis and staging of RCC.
  - If clinical presentation or ultrasound findings are suspicious for RCC, CT imaging is essential.
- MRI abdomen/pelvis
  - Modality of choice for diagnosis and staging in patients where contrast dye is contraindicated (due to renal insufficiency or allergy).

**Management**

- for confined disease:
  - partial or total nephrectomy depending on the tumour size
  - no role for adjuvant therapy after surgery
- for metastatic disease:
  - Targeted molecular therapy
    - receptor tyrosine kinase inhibitors (e.g. sorafenib, **sunitinib**)
      - ❖ first line therapy
      - ❖ have been shown to have superior efficacy compared to interferon-alpha
      - ❖ recommended by NICE as a treatment for advanced renal cell carcinoma.
      - ❖ Sunitinib is superior to interferon alfa in improving progression-free survival. Also, interferon alfa has significant toxicity.

**Prognosis**

- Prognosis is related to tumour staging:
  - the 5-year survival rate is around 80-100% in those with TNM stage-1 lesions, but this falls to 5-10% in those with stage-4 lesions
- Risk of distant relapse remains 30% for curatively resected renal cell carcinoma.

**Wilms' tumour**

- Wilms' nephroblastoma is one of the most common childhood malignancies.
- typically presents in children under 5 years of age, with a median age of 3 years old.
- primarily **composed of blastema**, which is primitive kidney mesenchyme.

**Features**

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- hypertension
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)
- Histologic examination is characterized by blastemal, stromal, and epithelial cells (triphasic tumor).

**Associations**

- Beckwith-Wiedemann syndrome
- as part of **WAGR** syndrome with Aniridia, Genitourinary malformations, mental Retardation
- hemihypertrophy
- **around one-third of cases are associated with a mutation in the WT1 gene on short arm of chromosome 11**

**Management**

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease

**prognosis:**

- good, 80% cure rate

## Angiomyolipoma

### Overview

- the most common benign tumour of the kidney
- is a benign hamartomatous tumor composed of blood vessels, smooth muscle cells and fat cells.
- caused by mutations in either the TSC1 or TSC2 genes, which govern cell growth and proliferation.

### Association

- commonly seen among patients with tuberous sclerosis.
- also commonly found in women with the rare lung disease lymphangioleiomyomatosis.

### Presentation:

- retroperitoneal hemorrhage (most frequent)
- unilateral flank mass.

### Diagnosis

- There are three methods of scanning that detect angiomyolipoma: ultrasound, CT and MRI.
- Ultrasound
  - is standard and is particularly sensitive to the fat in angiomyolipoma but less so to the solid components. However it is hard to make accurate measurements with ultrasound.
- CT
  - is very detailed and fast and allows accurate measurement. However, it exposes the patient to radiation and the dangers that a contrast dye used to aid the scanning may itself harm the kidneys.
- MRI
  - is safer than CT but many patients (particularly those with the learning difficulties or behavioural problems found in tuberous sclerosis) require sedation or general anaesthesia and the scan cannot be performed quickly.
- Biopsy
  - Some other kidney tumours contain fat, so the presence of fat isn't diagnostic. It can be difficult to distinguish a fat-poor angiomyolipoma from a renal cell carcinoma and a lesion growing at greater than 5 mm per year may warrant a biopsy in order to distinguish it from this form of cancer.

### Treatment

- Large angiomyolipoma can be treated with embolisation.
- do not normally require surgery unless there is life-threatening bleeding

## Bladder cancer

**Use of cyclophosphamide in granulomatosis with polyangiitis is associated with increased risk of bladder cancer (transitional cell carcinoma)**

### Epidemiology

- In the Western world
  - **transitional-cell (TCC) → 93% of bladder cancers**
  - squamous-cell carcinomas (SCCs) ➔ 6%
  - adenocarcinomas ➔ less than 1%
- male: female ratio 3:1
- women generally have a worse prognosis than men.

- At the time of diagnosis around 70% of carcinomas are still localised to the bladder, 20% extend to involve regional lymph nodes and 3% present with distant metastases

### Risk factors

- Risk factors for transitional cell carcinoma of the bladder include:**
  - Smoking
  - Exposure to aniline dyes in the printing and textile industry
  - Rubber manufacture →(exposure to nitrosamines (used in the manufacture of some cosmetics, pesticides, and in most rubber products))
  - Cyclophosphamide
- Risk factors for squamous cell carcinoma of the bladder include:**
  - Schistosomiasis
  - Calmette-Gurin (BCG) treatment
  - Smoking

### Diagnosis

- Cystoscopy is the gold standard for diagnosing bladder cancer.**

### Treatment

- Treatment of choice for localised tumours is transurethral tumour resection, with the use of intravesical chemotherapy.
- Intra-vesical instilling of BCG has virtually replaced cystectomy in the treatment of bladder carcinoma in situ.**

### Orthotopic bladder reconstruction for carcinoma of the bladder:

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation.**
  - Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common
  - Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons.
  - Associated electrolyte abnormalities may include hypokalemia, hypocalcaemia, and hypomagnesaemia.
  - it's usually improves with time and is mild.
  - treat metabolic acidosis with intravenous fluids and bicarbonate.
    - **Intravenous infusion of 1.26% sodium bicarbonate and potassium replacement**

### Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder).

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and **treat metabolic acidosis with intravenous fluids and bicarbonate**.

## Rhabdomyolysis

Collapse + ARF → rhabdomyolysis - treat with IV fluids

**Rhabdomyolysis can result from co-prescription of clarithromycin and statins**

### Overview

- Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission

### Pathophysiology

- muscle trauma or necrosis → **myoglobin** (a muscle protein), which may cause tubular damage or blockage, intense renovascular constriction, and local inflammation → Acute renal failure
- Rhabdomyolysis is strongly suggested by the fact that urinalysis is strongly positive for blood, whereas urine microscopy is negative for red blood cells.
  - The positive urinalysis is caused by **myoglobin**, a muscle protein released during muscle damage; this appears in the urine and can cause acute renal failure.

### Causes

- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy
- Crush injury: electrical injury, compartment syndrome, prolonged limb or tourniquet anaesthesia, extensive surgical dissection and infectious or inflammatory myopathies.
- McArdle's syndrome
- **Metabolic myopathy**
  - should be suspected when myoglobinuria is recurrent, associated with exercise or fasting and occurring with muscle cramps or weakness
  - **Carnitine palmitoyltransferase (CPT) deficiency is the commonest cause of inherited metabolic myopathy resulting in recurrent myoglobinuria**
  - The enzyme defect is diagnosed using ischaemic forearm testing and muscle biopsy, which demonstrates abnormal lipid or glycogen deposits
- Drugs:
  - statins (**should be stopped in any patient presenting with the syndrome.**)
    - Statins are metabolised via the **CYP3A4** pathway.
    - Drugs that inhibit its action and lead to excess statin toxicity include **macrolide** antibiotics such as clarithromycin.
    - It is important to note that atorvastatin (as a more hydrophilic agent) is less metabolised by CYP3A4 and hence the side effects of this combination are less profound.

### Features

The biochemical features of rhabdomyolysis are raised creatine kinase, hypocalcaemia (especially early after injury), hyperkalaemia and acute kidney injury.

- acute renal failure with disproportionately raised creatinine
- elevated CK, detectable a few hours after injury and peaks at the 48-h stage
- **myoglobinuria**, on urine dipstick (shows as haematuria),
  - Urine is dark due to myoglobin.

- Dipstick will be **positive for blood** (a false positive). On microscopy no red cells are seen although there may be pigmented granular casts.
- **Dipstick is the most quickly test for diagnosis**
- **hypocalcaemia** (myoglobin binds calcium)
- elevated phosphate (released from myocytes)
- hyperuricaemia
- **hyperkalaemia**
- metabolic acidosis in severe cases secondary to raised serum lactic acid levels from the ischaemic muscle fibres.
  - The serum lactate is raised which would suggest an acidotic picture over a normal blood gas picture

#### Management

- **IV fluids to maintain good urine output**
- urinary alkalinization is sometimes used

#### Loin pain-haematuria syndrome

- characterised by severe, unrelenting loin or flank pain and haematuria with **dysmorphic features suggesting a glomerular origin**
- A recent report suggested an important **psychological component** (unexplained somatic symptoms, an adverse psychological event preceding the onset of pain and a history of greater analgesic ingestion)
- One possible explanation for the haematuria in some patients is coexistent thin basement membrane disease.
- It was proposed that bleeding into and obstruction of the renal tubules was responsible for the loin pain
- Management
  - difficult to treat
  - Dependency on narcotic analgesia is common
  - Some patients undergo autotransplantation of the affected kidney in an attempt to relieve the pain

#### Renal tuberculosis

- accounts for 15-20% of extra-pulmonary tuberculosis
- **The combination of sterile pyuria, haematuria, dysuria and renal tract calcification is highly suggestive of renal tuberculosis**
- Many patients have refractory hypertension, which is renin-mediated and presumably due to segmental renal ischaemia
- **Excretion urography is the most helpful diagnostic investigation**, may show cavitating lesions in the renal papillary areas, commonly with calcification. There may also be evidence of ureteral obstruction with hydronephrosis

#### Xantho-granulomatous pyelonephritis (XGP)

##### Pathogenesis

- It develops as an abnormal macrophage response to infection, particularly in the presence of urinary tract obstruction, and is pathologically related to malacoplakia

##### Clinical features

- A flank mass is usually palpable, thereby distinguishing it from simple acute pyelonephritis or renal abscess, and occasionally mimicking renal cancer
- The disease is almost invariably unilateral
- Patients with XGP often appear chronically ill

- Symptoms include anorexia, fevers, weight loss and flank pain

#### Diagnosis

- The relatively rapid history, leukocytosis, renal impairment and positive urine culture make XPN much more probable than cancer
- **Computed tomography is the investigation of choice to confirm the diagnosis**, and it will show the replacement of renal parenchyma by rounded, low-density areas surrounded by a ring of enhancement; it will also establish the extent of the lesion (which may involve surrounding structures)

#### Prognosis and complications

- The course may extending over months or years
- AA amyloid may develop, resulting in the onset of nephrotic syndrome

### Vesico-ureteric reflux

#### Vesico-ureteric reflux management:

- in childhood: surgical intervention would be beneficial.
- When picked up in adulthood, the mainstay of management would be
  - ⇒ blood pressure control
  - ⇒ **Strict glycaemic control (reduce the frequency of recurrent infections and reduce the risk of progression to diabetic nephropathy.)**
  - ⇒ prompt treatment of UTI and careful surveillance during pregnancy.

- Vesicoureteric reflux refers to the retrograde flow of urine from the bladder to the upper urinary tract
- **It is the most common cause of recurrent urinary tract infections in children.**
  - ⇒ It is identified in approximately 40% of patients.
- This may occur due to incompetence of the valve at the vesicoureteric junction
- **It is most commonly detected the earliest in newborn girls**
- Present with recurrent UTI
- **Micturating cystourethrography is the most useful investigation** to check for vesicoureteric reflux during voiding in children. It is identified in approximately 40% of patients. (not useful in adult women because by this time the reflux tends to disappear)
- **the single most appropriate management for grade-V vesicoureteric reflux in child less than 1 year → Antibiotic prophylaxis**

grade	Age(year)	scaring	Initial treatment	Follow up
V	< 1	No	<b>Antibiotic prophylaxis</b>	Surgery
V	1-5	No	If unilateral: antibiotic prophylaxis	Surgery
V	1-5	No	If bilateral: surgery	
V	1-5	Yes	Surgery	
V	> 5		Surgery	

Grading of vesicoureteric reflux

grade	Description
I	Reflux into a non-dilated ureter
II	Reflux into the upper collecting system without dilatation
III	Reflux into a dilated ureter and/or blunting of calyceal fornices
IV	Reflux into a grossly dilated ureter
V	Gross dilatation of the ureter, renal pelvis and calyces; calyces show loss of papillary impression

## **Chronic reflux nephropathy (Chronic pyelonephritis)**

- **Chronic pyelonephritis** is also known as 'reflux nephropathy':
- starts in infancy or early childhood,
- predisposes to recurrent infections and progressive renal fibrosis and loss of function
- the kidneys are small, shrunken and scarred

### **Renal scarring**

- is a serious complication of chronic pyelonephritis that occurs due to vesicoureteric reflux.
- It is mediated by cytokines, chemokines and their receptors, complement, adhesion molecules and extracellular matrix proteins.
- **The cytokines which seem to play the largest role are:**
  - ⇒ interleukin (IL)-1beta,
  - ⇒ IL-3
  - ⇒ **Transforming growth factor (TGF)-beta.**
    - TGF-beta in particular seems to be **pro-fibrotic** by **recruiting fibroblasts**,
    - In a genotype where its production is limited has been shown to be less likely to develop renal scarring.
- Chronic reflux nephropathy should be suspected in the presence of multiple urinary tract infections, including during childhood
- may present with difficult-to-treat hypertension in young age
- **The investigation of choice is excretion urography (Micturating cystourethrogram),** which may show :
  - an irregular renal outline,
  - calyceal clubbing
  - and cortical scarring on the affected side
- The best course of action is to recognise this condition in childhood and consider surgical management where demonstrable ureteric reflux exists, or early intervention with antibiotics where repeat infection exists
- Chronic reflux nephropathy is a relatively common cause of end-stage renal failure in late childhood or early adult life if it goes unrecognized

### **Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis**

- |   |
|---|
| <ul style="list-style-type: none"> <li>• Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.</li> </ul>   |
| <ul style="list-style-type: none"> <li>• Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.</li> </ul> |

(European association of urology)

## Phimosis

- Phimosis is common in 2-year olds
- **Prognosis and management**
  - **Most will slowly dilate, thus Wait and watch is the most appropriate treatment**
  - In those who have persistent problems into teenage years, around 85% will respond to topical steroids, reducing the need for circumcision
  - Where there is obvious infection, a dorsal slit may be considered

## Urethral syndrome

- The condition is common in elderly postmenopausal women due to dryness and atrophy of the urethral tissue
- Presented with dysuria, increased frequency of micturition and sterile urine.
- **Treatment:** **Topical oestrogen cream often results in a dramatic response**

## Urinary tract infection (UTI) in adults

### Causes of UTI:

- **Escherichia coli** is the first most common
- **Staphylococcus saprophyticus** is the second most common cause of UTI in sexually active women

### Classification of UTI (European association of urology guidelines)

Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, <b>indwelling urinary catheters</b> , renal diseases, and/or with other concomitant immunocompromising diseases for example, <b>diabetes</b> .
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least <u>three UTIs/year</u> or <u>two UTIs in the last six months</u> .
Catheter-associated UTIs	UTIs in a person <b>currently catheterised</b> or has been catheterised <b>within the past 48 hours</b> .
Urosepsis	A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

### Features

- **classic symptoms of (UTI):** dysuria, frequency of urination, suprapubic tenderness, urgency, polyuria, haematuria
- **upper urinary tract infection (UUTI):** evidence of UTI with symptoms suggestive of pyelonephritis (loin pain, flank tenderness, fever, rigors or other manifestations of systemic inflammatory response).
- **lower urinary tract infection (LUTI):** evidence of UTI with symptoms suggestive of cystitis (dysuria or frequency without fever, chills or back pain).

### Diagnosis

- Diagnosis of UTI is primarily based on symptoms and signs. Bacteriuria or pyuria do not establish the diagnosis of UTI.
- **The gold standard test** for diagnosis of bacteriuria is culture of bladder **urine obtained by needle aspiration of the bladder** as it minimises the risk of contamination of the urine specimen.
  - All other techniques (urethral catheter and midstream specimens of urine) carry a higher risk of contamination and therefore produce some false positive results
- **Nitrite test:**
  - Gram negative organisms test positive on the nitrite test as they convert nitrates to nitrites for energy.
  - Gram positive organisms are unable to reduce nitrate to nitrite and therefore, test negative.
- UTI is usually diagnosed by a bacterial count of  $>100\ 000/\text{ml}$  at mid-stream urine (MSU)
- **Presentation with a first urinary tract infection associated with haematuria in elderly patient → Re-testing of urine with cytological examination after antibiotics**
- Sterile pyuria and negative urine cultures suggest urinary tract infection by the bacteria *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.
- Persistent haematuria should be investigated with excretion urography and cystoscopy

If the mid-stream urine (MSU) reveals bacteriuria, in asymptomatic pregnant lady, what is the most appropriate intervention?

→ Repeat sample

- NICE guidelines recommend a second confirmatory sample to be sent before initiating treatment.

### Recommendations for the diagnostic evaluation of uncomplicated cystitis

(European association of urology)

Diagnose uncomplicated cystitis based on:

- a focused history of lower urinary tract symptoms (dysuria, frequency and urgency);
- the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections.

Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis.

Urine cultures should be done in the following situations:

- suspected acute pyelonephritis;
- symptoms that do not resolve or recur within two-four weeks after the completion of treatment;
- women who present with atypical symptoms;
- pregnant women.

### Management (Sign.uk recommendations for UTI 2012)

- **Men**
  - ⇒ urine sample should be taken for culture.
  - ⇒ empirical antibiotics with a quinolone in men with symptoms suggestive of prostatitis.
- **Non-pregnant women**
  - ⇒ **LUTI**
    - Symptomatic bacteriuria → three-day course of trimethoprim or nitrofurantoin.

- Amoxicillin, ampicillin, nitrofurantoin and oral cephalosporins may be considered as alternatives
- **Routine urine culture is not required to manage**
- If not respond to trimethoprim or nitrofurantoin → urine for culture to guide change of antibiotic
- asymptomatic bacteriuria → Do not treat with an antibiotic.
- Recurrent UTI → consider using cranberry products to reduce the frequency of recurrence.
- ⇒ **UTI**
  - ciprofloxacin (7 days) or co-amoxiclav (14 days).
  - Acute pyelonephritis
    - ❖ hospital admission should be considered
    - ❖ the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days
- **Pregnant women:**
  - ⇒ **Treat symptomatic and asymptomatic UTI**
  - ⇒ Urine culture before starting empiric antibiotic and 7 days after completion empiric antibiotic treatment.
  - ⇒ **First line agent → Nitrofurantoin**
    - A dose of 50 mg QDS or 100 mg BD of modified release for 7 days is recommended.
    - Care for nitrofurantoin
      - ❖ elderly patients may be at increased risk of toxicity.
      - ❖ contraindicated in significant renal impairment. The BNF advises against its use in patients with GFR<60.
      - ❖ Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate).
  - ⇒ Second line → Trimethoprim
    - contra indicated in established folate deficiency, low dietary folate intake, or women taking other folate antagonists.
  - ⇒ Third line → cephalosporins
    - There is 20% cross-over with respect to allergy to penicillin and cephalosporins.
  - ⇒ **Complications**
    - **asymptomatic bacteriuria is associated with premature delivery and low birthweight.**
      - routine screening for asymptomatic bacteriuria at antenatal appointments is therefore recommended.
    - Infections in pregnancy should be treated, as 25% of patients will develop acute **pyelonephritis**

**UTI in diabetes**

- Data from the American Diabetes Association have shown that **9.4% of people diagnosed with type 2 diabetes had a UTI** compared to only 5.7% of those without.
- **The most common pathogens isolated from the urine of diabetic patients with UTI were *E. coli* and other Enterobacteriaceae such as *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and Enterococci.**
- **Infection with Extended spectrum beta-lactamase-producing *E. coli* (ESBL-producing *E. coli*) is an increasingly recognised cause of infection in diabetes patients and is associated with poor outcomes.**
  - **Carbapenems are generally considered the drug of choice for the treatment of ESBL/*E. coli* (ESBL-EC) infections**
    - ❖ With a half-life of 4 h, **ertapenem** is commonly used as it is administered only once daily.
  - Fosfomycin is an oral antibiotic agent that has broad activity against multi-drug-resistant pathogen, including ESBL-EC.
  - Another oral antimicrobial agent that can be considered for the treatment of ESBL-EC cystitis is nitrofurantoin.

**Extended spectrum beta lactamase (ESBL) urine infection → Intravenous meropenem**

**What is the next step in management of first episode of UTI in elderly after treatment with antibiotics?**

→ **Re-testing of urine with cytological examination after antibiotics**

- UTI may develop in patients with an underlying urothelial tumour.
- Persistent haematuria should be investigated with excretion urography and cystoscopy.
- Bladder tumours are around 50 times more common than tumours of the ureter or renal pelvis.

### **Antibiotic guidelines for urinary tract:**

The following is based on current BNF guidelines:

Condition	Recommended treatment
Lower urinary tract infection	Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin
Acute pyelonephritis	Broad-spectrum cephalosporin or quinolone
Acute prostatitis	Quinolone or trimethoprim

### **Asymptomatic bacteriuria (ABU)**

#### **Risk factors for asymptomatic bacteriuria**

- Female sex
- Sexual activity
- Comorbid diabetes
- Age
- Institutionalisation
- Presence of catheter

### Recommendations for the management of ABU (European association of urology)

- Do not screen or treat asymptomatic bacteriuria in the following conditions:
  - women without risk factors;
  - patients with well-regulated diabetes mellitus;
  - post-menopausal women;
  - elderly institutionalised patients;
  - patients with dysfunctional and/or reconstructed lower urinary tracts;
  - patients with catheters in the urinary tract;
  - patients with renal transplants;
  - patients prior to arthroplasty surgeries;
  - patients with recurrent urinary tract infections.
- Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.
- Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.
- Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect.

### UTI in childhood

- In up to 75% cases of single infection, no abnormality can be found
- Escherichia coli is the most common organism isolated (> 70% of cases)
- **Chronic diarrhoea or even acute diarrhoea can be a presenting feature** of childhood urinary tract infection
- Trimethoprim is often the best initial antibiotic of choice
- In children (particularly neonates and infants), UTI can be haematogenous and may be part of a septicaemic process, therefore, blood cultures and iv antibiotics are necessary

### Recurrent urinary tract infection (rUTI)

#### Definition

- two episodes of infection in six months, or three episodes in one year

#### Recurrent bacteriuria:

- **Relapse**
  - diagnosed by the recurrence of bacteriuria with the same organism within 7 days of completing antibacterial treatment and implies failure to eradicate infection.
  - usually occurs in conditions in which it is difficult to eradicate the bacteria, such as:
    - **renal stones,**
    - scarred kidneys,
    - polycystic disease or
    - bacterial prostatitis.
- **Reinfection**
  - occurs when bacteriuria is absent after treatment for at least 14 days, usually longer, followed by recurrence of infection with the same or a different organism.

#### Incidence

- annual incidence of a single UTI is 30 per 1000 women, with 44% experiencing recurrence within 12 months

#### Risk factor

Age-related risk factors for rUTI in women

Young and pre-menopausal women	Post-menopausal and elderly women
<ul style="list-style-type: none"> <li>• Sexual intercourse</li> <li>• Use of spermicide</li> <li>• A new sexual partner</li> <li>• A mother with a history of UTI</li> <li>• History of UTI during childhood</li> <li>• Blood group antigen secretory status</li> </ul>	<ul style="list-style-type: none"> <li>• History of UTI before menopause</li> <li>• Urinary incontinence</li> <li>• Atrophic vaginitis due to oestrogen deficiency</li> <li>• Cystocoele</li> <li>• Increased post-void urine volume</li> <li>• Blood group antigen secretory status</li> <li>• Urine catheterisation and functional status deterioration in elderly institutionalised women</li> </ul>

- **Sexual activity in young females**

- Recurrent cystitis may often accompany the onset of sexual activity in young females
- The appropriate first-line management is to advise strict attention to personal hygiene, and an increase in fluid intake and subsequent urine flow around times of sexual activity

- **Vesicoureteric reflux**

- **Chronic reflux nephropathy:**

- the best diagnostic investigation is → Micturating cystourethrogram

- **Posterior urethral valves**

- the chief complaint of children with this disorder is a poor urinary stream

- **Urinary tract obstruction in BPH:**

- post-void residual volume is the best way to estimate the degree of bladder obstruction

### Diagnosis of rUTI

- should be confirmed by urine culture.
- Do not perform an extensive routine workup in women with recurrent UTI without risk factors. (European association of urology)

### Treatment

- After treating the acute infection, **low dose antibiotics for 6-12 months** are the most evidence based **preventive measure** for recurrent (UTI) in women and are recommended by Scottish Intercollegiate Guidelines Network and the European Association of Urology guidelines as the standard of care.

### Prevention (European association of urology)

- Non-antimicrobial interventions
  - behavioural modifications
  - vaginal oestrogen replacement in post-menopausal women
  - Immunoactive Prophylaxis (in all age groups)
    - bacterial extracts to stimulate the host's immune system to produce antibodies
      - ❖ e.g. Oral immunostimulant OM-89
- Antimicrobial prophylaxis (continuous or post-coital)
  - When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used.
  - For patients with good compliance, self-administered short-term antimicrobial therapy should be considered.

## Catheter-Associated UTI

### Overview

- Once catheter is in place, the risk of bacteriuria Once catheter is in place:
  - short-term catheterization (ie, 2-4 days) → 10% - 30%
  - long-term catheterization → 90% -100%
- the most common source of gram-negative bacteraemia in hospitalized patients

### Causes

- Enteric pathogens (eg, ***Escherichia coli***) are most commonly responsible
- Proteus* and *Pseudomonas*** species are the organisms most commonly associated with **biofilm growth on catheters**.
- Candida***, especially ***Candida albicans***, is the **second-most-common organism** that can cause catheter-associated urinary tract infection or asymptomatic colonization

### Diagnosis

- diagnosis** of catheter-associated urinary tract infection can be made when the **urine culture** shows **100 or more CFU per mL** of urine from a catheterized patient.

### Treatment

- Symptomatic bacteriuria**
  - mild to moderate infections**: oral quinolones, usually for 10 to 14 days.
  - The recommended duration of therapy for **severe infections** is **14 to 21 days**.
- Asymptomatic bacteriuria**
  - not recommended**, with the following **exceptions**:
    - patients who are immunosuppressed after organ transplantation,
    - patients at risk for bacterial endocarditis and
    - patients who are about to undergo urinary tract instrumentation

## Urinary tract obstruction in children (posterior urethral valves)

### Overview

- A poor urinary stream suggests a urinary tract obstruction (usually infravesical)
- The most common cause in a male child is posterior urethral valves**
- posterior urethral valves**: symmetrical folds of urothelium extending distally from the prostatic urethra to the external urinary sphincter
- Renal dysplasia is usually associated with posterior urethral valves**

### Diagnosis

- The best diagnostic method is a micturating cystourethrography**
- The other option is endoscopy .

### Complications

- 30% of patients experience end-stage renal disease
- Vesicoureteric reflux occurs in half the patients