RENAL AT A GLANCE ebook 2023

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1: Disorders of Sodium

- GFR of 125 ml/min translates to filtration of 180 L fluid at the level of the glomeruli out of which 99% is reabsorbed by the tubules.
- >90% of the tubular water reabsorption is because water follows Na.
- All cells in the body including renal tubular cells are deficient in Na and high in K due to the basolateral Na K-ATPase which extrudes 3 Na and pulls in 2 K ions into the cells.
- CHECK THE PORTION UNDER SUB-HEADING ALDOSTERONE IN THE 'Disorders of K'

Counter-current mechanism and Vasopressin (ADH)

- Loop of Henle reabsorb up to 40% of total Na but only 25% of water as the thick ascending limb is permeable to Na but not water.
- This helps to maintain osmotic gradient from 290 mOsm/kg at cortex to 1200 mOsm/kg at tip of medulla.
- *ADH controlled reabsorption of water in the cortical duct is dependent on the above osmotic gradient.*
- ADH secretion is increased by increased in plasma osmolality and decrease in extracellular fluid volume.

Body water

- The average water content of adult human is approximately 60% of the body weight in males and 50% in females.
- *REMEMBER THAT HYPONATREMIA IS WATER EXCESS WHILE HYPERNATREMIA IS WATER DEFICIT*
- For hyponatremia
  - Water excess: 0.6W x (1- Na/140)
- For hypernatremia
  - Water deficit: 0.6W x ([Na/140]-1)
- W is weight in kg; serum Na is in mmol/L and replace 0.6 by 0.5 in women to get the total body water (TBW)

Hyponatremia

Usually caused by a failure to excrete water normally which in turn is due to inability to suppress ADH secretion.

- *Exception: psychotic patients with primary polydipsia are hyponatremic despite appropriately suppressed ADH release*
- Classified as hypovolemic, euvolemic (SIADH) and hypervolemic hyponatremia.

SIADH causes:

- Drugs: Carbamazepine, chlorpropamide, cyclophosphamide, SSRI and SNRI
- CNS causes: encephalitis, meningitis, brain tumours, brain abscesses, and stroke
- Pulmonary causes: Pneumonia, TB, aspergillosis, lung abscess, lung Ca
- Surgery
- HIV

SIADH diagnosis:

- Serum sodium <135mEq/L
- Serum osmolality < 275 mOsm/kg
- Urine sodium >40 mEq/L
- Urine osmolality >100 mOsm/kg
- The absence of clinical evidence of volume depletion
- The absence of other causes of hyponatremia - adrenal insufficiency, hypothyroidism, cardiac failure, pituitary insufficiency, renal disease with salt wastage, hepatic disease, drugs that impair renal water excretion.
- Correction of hyponatremia by fluid restriction

SIADH treatment:

- Fluid restriction
- Hypertonic saline in symptomatic with severe hyponatremia
- Salt tablet plus loop diuretic
- Tolvaptan (vasopressin receptor antagonist): beware of the hepatotoxicity.
- Urea
- Demeclocycline : beware of nephrotoxity, nausea, vomiting, photosensitivity and costs.

Hypernatremia

- Causes: Mostly due to decreased water intake
  - Impaired thirst due to hypothalamic disease
  - Sick and not drinking.
  - Severe skin or GI loss
- Even with large water losses, hypernatremia will not develop if thirst is intact, and water is available.
- Diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state: As hyperglycaemia and hypovolemia are corrected, the serum sodium will rise because of an osmotic shift of water from extracellular fluid into cells and loss of extra water in the urine as excess glucose is excreted (osmotic diuresis)

Treatment of hypernatremia:

- Water deficit calculation: 0.6W x ([Na/140]-1)
- Hypernatremia is chronic if it has been present for longer than 48 hours and do not decrease serum Na by more than 12 mEq/L in 24 hours.
  - Approx. 5% dextrose IV at 1.35 mL/kg/hour (maximum of 150 mL/hour)
- In acute hypernatremia (< 48 hours) more aggressive Na correction
  - 5% dextrose IV at 3-6 mL/kg/hour, up to a maximum of 666 mL/hour
- If struggling to get a line, give free water using NGT.

2: Disorders of Potassium

- Disorders of the renal tubules can lead to both metabolic acidosis/alkalosis and hypokalaemia/hyperkalemia
- K and H often move together- hyperkalemia predisposes to metabolic acidosis and vice versa; similarly metabolic alkalosis predisposes to hypokalemia
- BUT- hypokalemia can be associated with either alkalosis or acidosis
- All cells including renal tubular cells are low in Na, high in K and electronegative as the basal Na-K-ATPase pumps 3 Na out and pulls 2 K into cells

Aldosterone

- Aldosterone helps to reabsorb Na by the principal cells of the collecting duct
- Aldosterone helps to excrete K directly by the same principal cells
- Aldosterone helps to excrete H indirectly by the alpha intercalated cells of the collecting duct
- Net results of aldosterone action on tubular cells in CD:
    - directly reabsorb Na (and water passively)
    - directly excrete K
    - indirectly excrete H

H and K relation in the body

- Hyperkalaemia leads to metabolic acidosis by three mechanisms-
    - Excess K^+ enters the cell and in exchange H^+ comes out of cells
    - K^+ competes with H^+ for secretion by the collecting duct in exchange for Na+
    - Hyperkalaemia by decreasing renal ammonia production inhibits H^+ excretion in urine (ammonia is the chief buffer for urinary H^+)
- Metabolic acidosis leads to hyperkalaemia by-
    - Excess H^+ enters the cell and in exchange K^+ comes out of cells
    - H^+ competes with K^+ for secretion in exchange for Na+

Note: hypokalaemia causes alkalosis by augmenting the H-K-ATPase pumps which reabsorb K^+ and secrete H^+ in the type A intercalated cells in CD

Hypokalaemia associated with metabolic alkalosis

High BP

- Primary hyperaldosteronism (Commonest condition in this group)
- Liddle syndrome
- Chronic liquorice ingestion
- Apparent mineralocorticoid excess
- Familial Hyperaldosteronism (including Glucocorticoid remediable hyperaldosteronism [GRA])

Low-normal BP

- Bartter syndrome
- Gitelman syndrome (milder disease and commoner in adult population)

K and metabolic acidosis

- Hypokalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 1 (distal RTA)
  - Renal tubular acidosis type 2 (proximal RTA)
  - *Beware of chronic diarrhoea*
- Hyperkalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 4 (type 4 RTA

NOTE- Primary aldosteronism, Liddle syndrome, Chronic liquorice ingestion, apparent mineralocorticoid excess and GRA covered in eBook chapter on secondary hypertension.

Conditions presenting with hypokalaemia, metabolic alkalosis and low to normal BP.

Bartter syndrome

- Defect in Na^+ reabsorption in the TAL of loop of Henle
- Normal to increased urinary Ca
- Increased renal vasodilatory prostaglandins
- Treatment: NSAIDs, K supplementation and K-sparing diuretic e.g., spironolactone
- Often growth and mental retardation

Gitelman Syndrome

- Defect in thiazide-sensitive Na^+-Cl^- cotransporter in DCT
- Mostly a disorder of adulthood
- Low urinary Ca
- Hypomagnesaemia: high urinary Mg loss due to down regulation of Mg^+ channel TRPM6
- Treatment: K-sparing diuretic and Mg and K supplementation
- No growth or mental retardation

What can mimic Gitelman or Bartter syndromes i.e., present with hypokalemia, metabolic alkalosis and normal or low BP?

- Surreptitious self-induced vomiting
    - Urinary Cl^- is characteristically low as hypovolemia leads to increased Na^+ reabsorption with the accompanying Cl^- reabsorption
    - Often scarring on the dorsum of the hand and dental erosions
- Surreptitious diuretic use
    - Variable urinary Cl^- levels depending on the timing of diuretic use
    - Urine diuretic screen may be helpful

Renal tubular acidosis (RTA)

- Group of disorders characterized by normal anion gap metabolic acidosis with either hypokalemia or hyperkalemia and relatively well preserved GFR
- Normal anion gap metabolic acidosis with hypokalemia:
    - Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO3) in the proximal tubules
    - Distal RTA (type 1) caused by defects in distal H ion excretion
- Normal anion gap metabolic acidosis with hyperkalemia:
    - Type 4 RTA is due to either aldosterone deficiency or tubular resistance to the action of aldosterone and is the commonest among RTA

Proximal RTA (Type 2 RTA)

- Isolated defect in proximal HCO3 reabsorption or with impaired reabsorption of phosphate, glucose, uric acid, and amino acids (Fanconi syndrome)
- Urinary pH usually <5.5 due to compensatory increased H secretion by distal tubules
- Can be caused by myeloma due to tubular toxicity of the light chains
- Other causes include carbonic anhydrase inhibitors acetazolamide and topiramate, tenofovir, Wilson's disease, Cystinosis, Lowe syndrome, outdated tetracycline and lead or mercury poisoning
- Fanconi syndrome often suspected in normal anion gap metabolic acidosis with hypokalaemia, glycosuria AND low plasma phosphate and uric acid levels

Distal RTA (Type 1 RTA)

- Type 1 RTA is caused by inability of the distal tubules to secrete H
- Characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA
- Causes: **Sjogren's syndrome**, SLE, hypergammaglobulinemic states, primary biliary cirrhosis, autoimmune hepatitis, chronic obstructive uropathy, renal transplantation and glue sniffing
- Drugs causing RTA type 1: lithium, ibuprofen, ifosfamide and amphotericin
- Genetic associations: Marfan syndrome and Ehler Danlos syndrome

Treatment of Types 1 and 2 RTAs

- Alkali and potassium replacement
- Higher doses of alkali needed in type 2 RTA
- Potassium citrate useful in patients with hypokalemia or stones
- Patients with severe or symptomatic hypokalemia should be given potassium prior to or concomitantly with sodium bicarbonate therapy

Urine anion gap (UAG)

- UAG = Urine (Na + K − Cl)
- UAG is positive in healthy individuals
- With metabolic acidosis from any cause, the kidney will appropriately respond by excreting a heavy load of H *(except in type1 RTA where H excretion is characteristically defective)*
- NH3 in urine accepts H to form NH4 which combines with the negatively charge Cl to form NH4Cl
- UAG is positive in type 1 RTA (lack of H and hence low NH4Cl) and negative in metabolic acidosis due to any cause including diarrhea (excess H and hence high NH4Cl)

Type 4 RTA

- Normal anion gap metabolic acidosis and hyperkalaemia
- Hyporeninemic hypoaldosteronism as well as diminished tubular response to aldosterone
- Common in diabetics especially those with diabetic nephropathy
- Caused by ACEI, ARBs, K-sparing diuretics, Calcineurin inhibitors (cyclosporine and tacrolimus), NSAIDs, heparin, trimethoprim.
- May be seen in chronic interstitial nephritis of any cause or sickle cell disease
- Synthetic mineralocorticoid such as fludrocortisone may be effective.
- In patients with hypertension or fluid overload, thiazide or loop diuretic may help.

Hyperkalaemia

Causes

- Insulin deficiency in uncontrolled diabetes mellitus
- Acute on chronic kidney disease
- Drugs: ACE-I, ARB, CNI, heparin, trimethoprim, and nonselective beta-blockers (remember-beta1 receptors cause renin release and beta 2 activity drives K into cells)
- Type IV RTA
- Increased tissue catabolism e.g., in cytotoxic or radiation therapy or trauma
- Hyperkalemic periodic paralysis
- Digitalis overdose by inhibition of the Na-K-ATPase pump
- Red cell transfusion due to leakage of K out of cells during storage

Manifestations

- Ascending muscle weakness
- Cardiac manifestations and ECG changes:
    - Tall, peaked T waves with shortened QT interval
    - Followed by progressive lengthening of the PR interval and QRS duration and absent p wave
    - Finally, QRS widens further to a sine wave pattern
    - Cardiac conduction abnormalities and cardiac arrhythmias e.g., bradycardia, sinus arrest, VT, VF, and asystole
- Hyperkalemia can cause metabolic acidosis

Management

- Hyperkalemic emergency: muscle weakness or paralysis and cardiac conduction defects need cardiac monitoring and repeat testing of K every 1-2 hours
    - Administration of calcium chloride or gluconate (10 mL of a 10 percent solution) to antagonize the membrane actions of high K (cardio-protective) can be repeated every 30 to 60 minutes
    - IV insulin with glucose to drive extracellular K into cells
    - Salbutamol nebuliser
    - Ensure ceasing all drugs that can cause raised K- (ACEI, ARB, CNI, heparin, trimethoprim and NSAID)
- Used but of doubtful value in acute setting: Cation exchangers Patiromer (veltassa), and Sodium polystyrene sulfonate (resonium) which bind K in the GIT
- Loop diuretics with/without saline hydration
- IV sodium bicarbonate as correction of acidosis can lead to lower K
- Haemodialysis if conservative management fail

3. Acute Kidney Injury

Acute kidney injury (AKI) definition as per KDIGO guidelines

- Increase in SCr by > 0.3 mg/dl (26.5µmol/l) within 48 hours or >50% in 7 days
- Urine volume < 0.5 ml/kg/h for 6 hours

About AKI

- Pre-renal and post-renal forms are rapidly reversible with treatment
- Diagnosis of 'renal' causes often delayed (mostly because urine dipstick missed)
- Prognosis of AKI in the elderly :Data from US Renal Data System (USRDS)
  - Patients aged 67 years or older who developed AKI were 6.7 times more likely to develop ESRD by two years after discharge compared with those without renal injury
  - Patients with a history of CKD who developed AKI had a 41-fold increase in the risk of ESRD

Causes

Pre-renal causes (commonest in community-up to 70%)

- ***True volume depletion*** –gastrointestinal loss (vomiting, diarrhoea, bleeding); renal losses (diuretics, glucose osmotic diuresis); skin or respiratory losses (insensible losses, sweat, burns); third space sequestration (crush injury)
- ***Hypotension*** – Decreased BP from shock (hypovolemic, myocardial, or septic)
- ***Drugs*** – Cause pre glomerular vaso-constriction i.e., NSAIDs, Calcineurin inhibitors (cyclosporine, tacrolimus) OR post glomerular dilatation i.e. ACE-inhibitors or angiotensin II blockers OR cause volume depletion i.e. diuretics
- ***Oedematous states-*** decreased cardiac output in CCF and splanchnic venous pooling and systemic vasodilation in cirrhosis causing reduced renal perfusion (Hepatorenal syndrome)

Renal causes of AKI (intrinsic renal pathology)

- ***Glomerular:*** Glomerulonephritis, thrombotic microangiopathy, vasculitis
- ***Tubulo -interstitial:*** The commoner acute tubular necrosis (**ATN**) and acute interstitial nephritis **(AIN)**

ATN- defined by histologic changes- necrosis of the tubular epithelium and occlusion of the tubular lumen by casts and cell debris; 3 major causes of ATN are:

- *Renal ischemia — All causes of severe prerenal AKI particularly hypotension, shock and surgery*
- *Sepsis- Usually associated with hypotension*
- *Nephrotoxins- aminoglycosides, vancomycin, cisplatin, radiocontrast material, cidofovir*

- *Post renal cause of AKI*
- Any cause of obstruction to urine flow downstream of kidneys:
    - Ureteric obstruction (bilateral), bladder neck or urethral obstruction e.g. stone, clot, enlarged prostate
    - Ureteric obstruction to a single functioning kidney

Causes of AKI in hospitalised patients

- **ATN – 45 percent**
- Prerenal disease – 21 percent
- Acute superimposed on CKD – 13 percent
- Urinary tract obstruction – 10 percent (most often older men with prostatic disease)
- Glomerulonephritis or vasculitis – 4 percent
- AIN – 2 percent
- Atheroemboli – 1 percent
- **Remember: Prerenal causes lead to 70% of community AKI**

Evaluation of AKI

- **History**: diarrhoea/vomiting/recent radiocontrast exposure/starting or increased dose of diuretics/ACEI or ARBS/antibiotics/urinary stones/NSAIDs/herbal medicines etc.
- **Physical examination**: volume status as hypovolemia suggests pre-renal cause while euvolemia suggests renal or post renal cause
- **URINE DIPSTICK** : should be considered part of initial renal evaluation as haematuria/proteinuria may suggest renal cause of AKI i.e. GN
- **Rule out obstruction with USG**
- **EUC**- for diagnosis/monitoring progress ; high K requires urgent medical therapy and/or dialysis
- **GFR** not useful in the acute setting; look at the creatinine trend
- **FBC**- disproportionate anaemia may indicate underlying myeloma or microangiopathic haemolytic anaemia e.g. HUS or TTP
- **Myeloma screen**
- **LFT** - if abnormal may indicate possibility of Hepato-renal syndrome (HRS)
- **Coagulation** - If abnormal may indicate sepsis or HRS. A normal coagulation profile is pre-requisite for renal biopsy or central line insertion for dialysis
- **Blood gas** - For assessing acid base status which may indicate need for dialysis
- **Renal biopsy** when renal cause suspected e.g., GN, nephrotic syndrome, TTP, HUS etc.
- **Send urine for dysmorphic red blood cells and RBC casts if haematuria seen** (with no evidence of UTI, stones or anatomical lesions on USG)

- **White cell cast** may indicate AIN

Presence of dysmorphic RBCs or RBC cast in urine- **GN**

- **Serum complements** (low in post-infectious nephritis, lupus nephritis, nephritis associated with endocarditis and cryoglobulinemia)
- **Blood cultures and antistreptococcal antibodies** in case of suspicion of post infectious GN when there is history of preceding pharyngitis or impetigo
- **ANA, ENA, Ds-DNA** to exclude lupus nephritis
- **Hepatitis and myeloma screen** (to exclude cryoglobulinemic nephritis and mesangio-capillary glomerulonephritis)
- **ANCA** (rule out vasculitis e.g.PR3 ANCA positive granulomatosis with polyangiitis and MPO ANCA positive microscopic polyangitis)
- **Anti-GBM antibody** to rule out Goodpasture syndrome

Treatment of AKI

- Fluid resuscitation
- Monitoring of urine output, fluid balance chart and daily weight to assess volume status (DO NOT NEED CATHETERISATION ROUTINELY)
- Cease nephro-toxic and non-essential medications e.g. ACE inhibitors, ARBs, diuretics, NSAIDS, aminoglycosides and sometimes drugs that can cause interstitial nephritis e.g. antibiotics, PPIs like omeprazole
- Metformin is in itself not nephrotoxic but as it is renally cleared, it is held to protect against lactic acidosis given that many of these patients are acidotic.
- Dose adjustment of drugs as per changing renal function to avoid accumulation with resultant toxicity.
- Urgent antibiotic treatment initiation if sepsis suspected.
- Treat the underlying cause e.g. hypercalcemia in myeloma causing AKI needs aggressive hydration while cast nephropathy in myeloma causing AKI needs urgent steroids/anti myeloma treatment
- *Recovery phase of ATN: Patient may have marked polyuria as tubular recovery lags; patient will need sufficient fluid replacement to prevent second hit of AKI from dehydration.*
- Complications refractory to medical treatment - where dialysis is indicated:
    - Refractory hyperkalaemia especially with ECG changes
    - Pulmonary oedema
    - Acidosis (pH < 7.15)
    - Uraemic encephalopathy

- Uraemic pericarditis

- No known pharmacological therapy known to cure AKI

Some specific forms of AKI

Radiocontrast nephropathy

- Usually reversible form of ATN
- >25% increase in SCr in 48 hours without another identifiable cause
- Risk factors:

Pre-existing CKD or low renal perfusion (e.g. CCF, dehydration)

Age >70

Multiple myeloma

Diabetes

Volume and type of contrast media used (high osmolar contrast more nephrotoxic)

Inpatients (? independent risk factor)

Drugs like NSAIDs, ACE inhibitors and ARBs

- Clinically different from other forms of AKI as usually presents as ATN within 24 - 48 hours of contrast administration and improvement within three to seven days
- Treatment- avoid nephrotoxins, pre and post IV hydration with 0.9% saline or NaHCO3
- No longer recommended: oral NAC
- Use the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium

Atheroembolic renal disease

- Cholesterol crystal embolization to the kidneys
- Usually after coronary angiography or angioplasty (commonest) , renal angiography or cardiovascular surgery, thrombolytic therapy, or anticoagulation
- AKI several weeks later (sometimes within 1-2 weeks)
- Urine bland
- Cyanosis or discrete gangrenous lesions in the toes with intact peripheral pulses (blue toes), livedo reticularis, GI symptoms with pain/bleed, focal neurologic deficits, orange plaques in the retinal arterioles(Hollenhorst plaques)
- May have eosinophilia, eosinophiluria, and hypocomplementaemia.

- Definitive diagnosis by renal biopsy showing *cleft like spaces within arteries (cholesterol ghosts)*
- Supportive therapy and secondary prevention of CV disease with aggressive lipid lowering therapy.

Acute Interstitial Nephritis (AIN)

- Caused by inflammatory infiltrate in the renal interstitium (glomeruli normal)
- Associations:
    - **Drugs** (antibiotics, NSAIDs, diuretics and PPIs) – 70 to 75%
    - **Infections** (streptococcus, legionella, CMV etc.) – 4 to 10%
    - **Tubulointerstitial nephritis and uveitis (TINU) syndrome** – 5 to 10 %
    - **Systemic disease** including sarcoidosis, Sjogren's syndrome, SLE and others – 10 to 20 %
- **Presentation:**
    - May present from few days to months after drug exposure
    - Rash – 15 %; Fever – 27 %; Eosinophilia – 23 %
    - Triad of rash, fever, and eosinophilia – 10 %
- **Diagnosis:**
    - History/above presentation/urine showing white cells or white cell casts and sometimes eosinophiluria indicate diagnosis
    - Renal biopsy definitive but usually not be needed
- **Treatment:**
    - -Discontinuation of the potential causative agent is mainstay of therapy
    - 2-3 months course of prednisolone in those whose creatinine does not improve within 7 days of stopping offending drugs

Gentamicin and renal toxicity

- Aminoglycosides freely filtered across glomerulus and partially taken up by the proximal tubular cells.
- Gentamicin levels inside PTC cells 100 to 1000 times serum levels……toxic to the cells
- Non-oliguric AKI due to ATN usually occurs 5-10 days after treatment.
- Once daily dosing better from the nephrotoxicity perspective: higher peaks for shorter periods and prolonged period of very low exposure may allow for more efficient handling and excretion.
- Hypomagnesaemia, hypocalcaemia, hypophosphatemia and hypokalaemia may be seen due to tubular defects.

Heme Pigment Nephropathy (in rhabdomyolysis and hemolysis)

- Myoglobin and haemoglobin are filtered by the glomerulus into the urinary space and degraded releasing **heme**
- Dipstick-positive haematuria in the absence of any RBC by microscopy may be the first clue along with pigmented granular casts
- Heme can lead to AKI by three processes:
    - Tubular obstruction, possibly in association with uric acid
    - Direct proximal tubular cell injury
    - Vasoconstriction leading to medullary hypoxia

- Also, in rhabdomyolysis sequestration of large amounts of fluid in the injured muscle can cause hypovolemia and pre renal AKI
- Treatment consists of fluid replacement and at times alkaline diuresis with intravenous bicarbonate to reduce chances of tubular obstruction

4. Chronic Kidney Disease

- Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for > 3 months irrespective of the cause
- DM and HTN are responsible for up to two-thirds of the cases of CKD followed by glomerulonephritis and ADPKD
- The glomeruli of all CKD patients go through a phase of glomerular hypertension, hyperfiltration and hypertrophy due to activation of renin-angiotensin-aldosterone system
- Cardiovascular disease is the leading cause of mortality in patients with CKD
- Referral to nephrologist when eGFR < 30 mL/min and/or proteinuria > 0.5 g/24 hours
- Living donor pre-emptive renal transplantation should be considered in patients with CKD when the GFR is <20 ml/min/1.73 m^2

Consequences of loss of renal function with CKD

- RAAS activation leads to raised glomerular blood flow and pressure and therefore raised glomerular filtration i.e., adaptive hyperfiltration in the good nephrons.
- In early CKD, the raised GFR helps to maintain serum creatinine in normal range
- **Vicious cycle:** Sustained glomerular hyperfiltration leads to compensatory hypertrophy and eventually damaged nephrons.
- Complications of CKD
  - FLUID, ELECTROLYTE AND ACID/BASE: *Fluid overload, hyperkalaemia, metabolic acidosis*
  - CARDIOVASCULAR **(leading cause of mortality):**
    - *Hypertension:* Data from the MDRD study showed that prevalence of HTN rose from 65 to 95 percent as the GFR fell from 85 to 15 mL/min
    - *Coronary heart disease:* accounts for **40 to 50% of mortality in dialysis patients**
    - *Strokes, Arrhythmias and Sudden Cardiac Death (SCD):* Dialysis patients have a 5-10-fold higher relative risk of stroke and SCD accounts for about **one-fourth of all deaths among dialysis patients.**
  - ***HAEMATOPOIETIC:*** Anaemia due to insufficient production of erythropoietin and increased risk of bleeding from platelet dysfunction
  - BONE AND MINERAL METABOLISM: *High turnover bone disease , low turnover bone disease(adynamic bone disease) and dialysis related amyloidosis*
    - Initial step in the pathogenesis is phosphate retention which starts when GFR is below 70 ml/min followed by hypocalcaemia, raised PTH, decreased 1,25-dihydroxyvitamin D (calcitriol) concentration, high FGF concentration and repression of calcium-sensing receptors (CaSRs) in the parathyroid gland
    - High turnover bone disease- Due to high serum PTH levels
    - Low turnover bone disease (adynamic bone disease)- In patients with CKD stage 5, and on dialysis, adynamic bone disease is now the commonest renal bone disease and is the consequence of over-suppression of PTH; AIM for PTH levels at 2-7 times the upper limit of normal to prevent this condition.

- Dialysis related amyloidosis: deposition of amyloid almost exclusively seen in dialysis patients, present with shoulder pain or carpal tunnel syndrome.

- ***NEUROLOGIC:*** *Uremic encephalopathy, dialysis disequilibrium syndrome, neuropathy, and sleep disorders*

  - *Dialysis disequilibrium syndrome (DDS):* Usually seen when patients have rapid reduction in their urea levels due to urgent haemodialysis.
  - Present with headache, nausea, confusion, seizures or even coma
  - To prevent DDS, dialysis started with short durations and low blood flow rates

- ENDOCRINE: *Reduced renal clearance of insulin with advanced CKD*

  - As GFR falls below 15 to 20 mL/min, reduction in renal clearance of insulin- patients either need smaller doses of insulin/oral hypoglycemics or sometimes do not need them anymore.

- SKIN: *Calcific uremic arteriopathy (calciphylaxis), uremic pruritus and nephrogenic systemic fibrosis (NSF)*

- *Calcific Uremic Arteriopathy (Calciphylaxis): Estimated 6-month survival of approximately 50 percent*

  - *Systemic medial calcification of the arterioles leading to ischemia and subcutaneous necrosis.*
  - Excruciatingly painful lesions tend to occur in areas with large. amounts of subcutaneous fat such as thigh, abdomen, and buttock
  - Risk factors: High serum phosphate and PTH, Obesity, DM, female sex, white ethnicity, hypercoagulable states such as protein C and S deficiency and antiphospholipid syndrome, hypoalbuminemia, and the use of drugs such as warfarin, vitamin D, calcium-based phosphate binders and systemic glucocorticoids
  - Treatment involves intravenous sodium thiosulphate, hyperbaric oxygen, wound care, optimisation of dialysis, avoid warfarin and treat hyperphosphatemia
  -

- Nephrogenic Systemic Fibrosis (NSF): Scleroderma-like disorder seen in patients with CKD, AKI and failing kidney transplant following exposure to gadolinium (Gd3+) containing agents used in MRI scans

  - Although the usual time period between exposure to Gd3+ and manifestation of NSF is 2 to 4 weeks, cases have presented after years
  - Bilateral flexion joint contractures can occur in up to 70 percent of patients and ffibrosis can affect internal organs like the lung and heart
  - No known treatment
  - Gd3+containing contrast should be avoided with GFR< 30 ml/min

Management of CKD

- Referral to nephrologist when eGFR < 30 mL/min and/or proteinuria > 0.5 g/24 hours

- Good HTN management with either ACEI or ARB especially in the presence of proteinuria
- Aim for HbA1c < 7.0%, good lipid control, metformin should not be used when the GFR is less than 30 ml/ min/ 1.73m^2)
- Role of SGLT2 inhibitors in slowing CKD progress
- Anemia
    - Serum ferritin < 500 ng/ml and/or transferrin saturation < 30% should receive parenteral iron
    - Erythropoiesis stimulating agents (EPO) started after ensuring adequate iron stores when Hb < 100 g/L
    - Hold EPO when Hb > 130g/L as at greater risk for increased cardiovascular mortality and stroke

- ***CKD MBD (mineral and bone disorders)***
    - *Phosphate binding agents*
        - Ca containing binders: Potential for hypercalcaemia and soft tissue calcification, calcific uremic arteriopathy
        - Non-calcium containing binders : sevelamer, lanthanum carbonate, and sucroferric oxyhydroxide.
- ***High PTH***
    - *Calcimimetic* - Cinacalcet: mimics the action of increased Ca on the Ca sensing receptor (CaSR) on the parathyroid gland and therefore inhibit PTH secretion.
    - Use associated with hypocalcaemia and adynamic bone disease due to excess suppression of PTH

- ***TREATMENT OF ACIDOSIS***
    - Patients with serum bicarbonate <20 meq/L should receive alkali supplementation.
    - Alkali supplementation is associated with slower decline of GFR

- ***VACCINATION IN CKD***
    - Generally reduced response to vaccination
    - All CKD patients with GFR < 30 ml/min should be vaccinated against pneumococci, hepatitis B and influenza
    - Annual inactivated influenza vaccine (live influenza vaccine is contraindicated in CKD)

5. Peritoneal Dialysis

- Despite evidence that peritoneal dialysis (PD) is associated with early survival advantage over Haemodialysis (HD) and better quality of life, PD utilization is far lower than that of HD.
- PD utilises both Diffusion and Ultrafiltration that occurs across the semipermeable peritoneal membrane. For achieving ultrafiltration, the PD fluid typically contains high concentrations of dextrose, that creates an osmotic gradient to drive ultrafiltration.
- There is constant lymphatic absorption of PD fluid through lymphatic channels in the diaphragm that impacts on the nett amount of fluid that is removed during a PD exchange.
- Understanding peritoneal membrane transport characteristics helps in PD prescription.
- Peritoneal membrane transport characteristics can be assessed using the peritoneal equilibration test.
  - Patients with peritoneal membrane characterised as low transporter – have poor solute clearance but better ultrafiltration because the osmotic gradient is maintained for a longer time though the dwell. These patients do well with long exchanges that are typically delivered by CAPD with manual exchanges
  - The opposite is true for patients with peritoneal membrane classified as high transporters and these patients do well with short exchanges typically delivered by APD using a cycler at night.
- Patients on APD have lower rates of peritonitis as compared to those on CAPD. There is no other difference in outcomes between the 2 modalities.
- High concentrations of dextrose in PD bags have adverse metabolic consequences as well as toxic effects on the peritoneal membrane due to deposition of glucose degradation products.
- 7.5% Icodextrin is a dextrose sparing agent that achieves similar ultrafiltration as a 4.5% dextrose containing PD bag
  - Icodextrin is used only for long dwells and is not licenced for use in more than 1 PD exchange a day.
  - Icodextrin is associated with better HbA1C levels in diabetic patients on PD and less hospitalisations from fluid overload. There is also emerging evidence that it is associated with lower mortality.
  - Some glucometers that are based on glucose dehydrogenase reaction to measure blood glucose levels can overestimate of blood glucose levels in patients on Icodextrin (and miss hypoglycemia). In addition, patients on Icodextrin may have underestimation of serum amylase levels and can miss acute pancreatitis.
- Providing adequate dialysis is only one of the many components of prescribing high quality -goal directed PD.
- Residual kidney function contributes significantly towards solute clearance and maintaining euvolemia in patients on PD.
- Low GDP, neutral pH PD solutions have been shown to preserve residual kidney function and urine output and are associated with less inflow pain. These fluids do not have any significant impact on other outcomes, including technique survival or mortality.

- Other factors that preserve residual kidney function include use of ACEi/ARBs for treatment of hypertension, avoiding prolonged use of aminoglycosides, NSAIDs and NSAIDS and radio-iodine contrast agents
- Peritonitis remains an important cause of morbidity, hospitalisations, technique failure and mortality in patients on PD. The updated ISPD 2022 Guidelines recommendations on prevention and treatment of PD related peritonitis can be accessed here: https://journals.sagepub.com/doi/pdf/10.1177/08968608221080586
- Peritonitis treated with IP antibiotics has better outcomes as compared to IV antibiotics, unless the patient has systemic signs of sepsis.
- Intermittent IP administration of antibiotics in one PD exchange a day has similar response rates as continuous IP administration of antibiotics in every PD exchange.
- Every hour of delay in administering antibacterial therapy from time of presentation to hospital increases the risk of PD failure or death by 6.8%.

6. Haemodialysis

- Haemodialysis (HD): solute composition of blood is altered by exposing it to another solution (dialysate) across a semipermeable membrane
- Two main mechanisms involved in solute and water removal:
  - Diffusion: Solutes removed by random molecular motion
  - Ultrafiltration (convective transport):Positive hydrostatic pressure causes solutes to be dragged along with water across the semipermeable membrane
- ***High efficiency membrane***: A bigger membrane leads to better solute clearance.
- ***High flux Membrane***: Larger pores allow passage of larger molecules like B2-microglobulin and more water.
- ***Hemofiltration (HF)***: uses only convection and no diffusion.
  - large volume of replacement fluid (25 to 50 L per day) infused into either the inflow or outflow blood line and both this replacement fluid and excess fluid in the patient are removed by UF
  - Larger sized molecules cleared better by HF in comparison to HD
  - Used in the slow, continuous renal replacement therapies (CRRT) for the sick and hypotensive patient in ICU
  - No dialysis fluid (dialysate) needed
- Hemodiafiltration (HDF) utilizes convective in combination with diffusive clearance i.e., combination of HD and HF
  - HDF allows increased clearance of larger-molecular-weight molecules compared to HD
  - Better tolerated in those with lowish BP
  - More expensive than HD

Vascular access in HD

- Needs to be able to support a dialysis circuit flow of 300mL/minute
- Preference serially
  - AV fistula: An AV fistula is a deliberate connection between a native artery and vein and is typically constructed with an end-to-side, vein-to-artery anastomosis
  - AV grafts: Constructed by interposing graft material between an artery and vein.
  - Tunnelled dialysis catheters: Tunnelled, cuffed central venous access dual-lumen catheters
  - *NOTE: AV fistulas associated with the lowest complication rates*

Dialysis catheter related bacteraemia

- Average rate is 1 episode per 1000 catheter days (2-3 years) for a tunnelled line VS AV fistula rate of infection is 1 per 30-40 years
- 40-80% gram positive for coagulase negative staphylococcus or s. aureus
- S aureus CRB associated with ***20-30% mortality***
- 'Around catheter' contamination more common than 'inside catheter'
- Higher in
  - Patients with diabetes
  - Non tunnelled lines
  - Femoral>internal jugular>subclavian

HD dosing and prescription

- More dialysis is better, but one has to be realistic
- Dialysis is never truly 'adequate'(does 10-15% of what normal kidneys do)
- The most effective way of providing more dialysis is by longer duration treatments
- Basic HD prescription incorporates
    - Frequency and duration
    - Anticoagulation
    - Targeted dry weight (enables calculation of fluid removal)

Dialysis Initiation

- Average GFR at initiation is 5-10mL/minute
- Conventional indicators are
    - Fluid overload
    - Hyperkalaemia
    - 'Uraemia'
    - Pericarditis

HD related complications

- **Intradialytic Complications**
    - Hypotension – 25 to 55 percent of treatments
    - Cramps – 5 to 20 percent
    - Nausea and vomiting – 5 to 15 percent
    - Headache – 5 percent
    - Chest pain – 2 to 5 percent
    - Back pain – 2 to 5 percent
    - Itching – 5 percent
    - Fever and chills – <1 percent
- **Interdialytic Complications**
    - Fluid overload
    - Hyperkalaemia
    - Thrombosis of a haemodialysis catheter or arteriovenous access

Intradialytic hypotension: possible causes:

- Target or dry weight set too low: extent of ultrafiltration is too high
- Rate of ultrafiltration is too fast
- Rate of plasma refilling is too slow
- 'Reverse plasma refill': more likely when the pre-dialysis urea, glucose or sodium (contributors of plasma osmolality) are excessively high
- Mechanisms to maintain blood pressure during dialysis are impaired (usually due to diminished cardiac reserve or autonomic neuropathy)

Intradialytic muscle cramps

- Hypotension, hypovolemia (excessive fluid removal), need for high ultrafiltration rate (due to excess water intake in the interdialytic period) lead to vasoconstriction, resulting in muscle hypoperfusion leading in turn to impairment of muscle relaxation.
- Pre-dialysis Quinine or carnitine supplementation used for management.

Intradialytic haemolysis

- Usually presents with chest pain or tightness, backpain, and dyspnoea.
- Signs include port-wine appearance of the blood in the venous line, pink discolouration of plasma in centrifuged specimens, rapidly falling haematocrit and sometimes a dramatic deepening of skin colouration
- Causes include:
    - Overheated dialysis solution
    - Hypotonic dialysis solution
    - Dialysis solution contamination with formaldehyde, bleach, chloramine, fluoride or nitrates from the water supply and copper from copper tubing or piping
    - Blood line obstruction or narrowing due to kinks
- If not detected early, haemolysis can lead to severe hyperkalaemia due to release of potassium from the damaged erythrocytes
- Stop dialysis immediately, clamp the blood lines (to prevent return of blood to avoid increasing the risk of hyperkalaemia)

Dialysis prognosis

- According to the United States Renal Data System (USRDS) 2018 report, for patients starting dialysis in 2011, the adjusted five-year survival from day 1 was 52 percent for patients on peritoneal dialysis and 42 percent for those on haemodialysis (worse in DM)
- Observed survival is best in patients treated with home hemodialysis:
    - 89 percent at 5 years
    - 74 percent at 15 years in nondiabetics
    - 50 percent at 15 years overall

7. Nephrotic Syndrome

- Nephrotic syndrome is a constellation of clinical and biochemical features which include heavy proteinuria (> 3.5g/day), hypoalbuminemia (<25g/L) and oedema. Also frequently observed are hyperlipidaemia and hypercoagulability with thrombotic events.

- The following conditions can lead to presentation with nephrotic syndrome:

Four Primarily Glomerular pathologies

  - Minimum Change Disease (MCD)
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranous Nephropathy (MN)
  - Membranoproliferative (MPGN)/Mesangiocapillary (MCGN):)-

can be nephrotic or nephritis

Systemic diseases

  - Diabetes Mellitus
  - Amyloidosis

Basic differences among the 4 glomerular pathologies causing nephrotic syndrome are as follows: remember renal biopsies are assessed by light microscopy (LM), electron microscopy (EM) and immunofluorescence (IF)

- MCD: **Podocyte foot process effacement** on EM (normal LM and IF)
  - *Mesangium, and endothelium completely normal with no sub-epithelial or endothelial deposits*
- FSGS: LM shows **sclerosis** in parts (segmental) of some (focal) glomeruli with EM showing **foot process effacement** (normal IF)
- MN: **Thickened GBM with no cellular proliferation on** LM; EM show **sub-epithelial deposits** (spikes and domes with thickened GBM) and IF shows IgG
  - *Mesangium and endothelium characteristically normal and no sub-endothelial deposits*
- MCGN (MPGN): **Mesangial and endocapillary cellular proliferation** (*manifests as difficult to visualise capillaries as glomeruli often full of cells*)) **with thickened GBM leading to a double-contour** (tram track) appearance of glomerular capillary walls
  - EM may show **both subepithelial and subendothelial deposits**
  - IF may show Ig or only C depending on the type (immune vs complement mediated MCGN)

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS)

- MCD is characterised by diffuse foot process effacement on electron microscopy (EM) in the absence of any findings on light microscopy (LM) or Immunofluorescence (IF)
- About 90% of nephrotic syndrome in children is caused by MCD while it is seen in only 10-15% of adults with nephrotic syndrome
- MCD among all causes of nephrotic syndrome is most likely to present acutely (over days to a week or two)
- MCD shows better response to treatment with corticosteroids in children than adults
- FSGS is a histologic pattern of glomerular injury characterised by sclerosis in parts (segmental) of some (focal) glomeruli and is the commonest cause of nephrotic syndrome in adults of African origin

- FSGS may be primary or secondary to genetic mutations in podocyte proteins, viral infections, drug toxicity, maladaptive response to reduced number of functioning nephrons due to any renal disease e.g., DM, SLE or any GN
- 40-60% of primary FSGS cases achieve partial or complete remission with corticosteroids
- Both MCD and FSGS are associated with diffuse foot process effacement; due to the focal nature of FSGS it may be mistaken for MCD if not enough glomeruli are visualised in biopsy
- About 30% of FSGS recurs in the transplanted kidney

Membranous nephropathy (MN)

- MN is characterised by typical sub-epithelial electron dense deposits on EM (absence of endothelial or mesangial changes) which stain for IgG and complement components on IF
- MN is the commonest cause of nephrotic syndrome in the Caucasian adult population and while up to two thirds of cases of MN are primary or idiopathic, the following conditions and agents are associated with MN :
  - Autoimmune disorders: SLE (common), rheumatoid arthritis, Sjogren's syndrome, Grave's disease, Dermatomyositis, Mixed connective tissue disorder, Systemic sclerosis
  - Infections: Hepatitis B (common), Hepatitis C, Schistosomiasis, Malaria, Leprosy, Filariasis
  - Drugs: Gold, Penicillamine, NSAIDs, Captopril
  - Malignancy: Solid organ tumours e.g., prostate, lung or colon, less commonly haematological malignancies like CLL
  - Others: Renal transplant, Sickle cell disease, Sarcoidosis
- 70% of cases of idiopathic MN have circulating auto-antibodies against phospholipase A2 receptor (PLA2R) located on the surface of podocytes.
- The phospholipase A2 receptor (PLA2R) antibody titres are useful both diagnostically and prognostically.
- Patients are categorised into low, medium or high risk depending on level of proteinuria, renal function and anti- PLA2R antibody levels
  - *Immunosuppressive therapy with glucocorticoids plus cyclophosphamide, Rituximab or CNI (cyclosporine or tacrolimus) offered for those in the high risk and majority of moderate risk categories*

Membranoproliferative/ Mesangiocapillary glomerulonephritis (MPGN/MCGN)

- Characterised by increased mesangial and endocapillary hypercellularity (proliferative lesions) with thickening of the GBM often leading to a double contoured appearance
- Classified as immune-complex–mediated or complement-mediated as follow:
  - Immune complex mediated MCGN: '*chronic antigenemia causing activated classical complement pathway*'
    - -Infections: **HCV (often causing cryoglobulinemia), HBV**, Infective endocarditis, HIV, malaria, schistosomiasis
    - -Autoimmune disorders: **SLE**, Sjogren's syndrome, Rheumatoid Arthritis
    - -Monoclonal Gammopathies: **Myeloma, MGUS, MGRS**

- Complement mediated: '*persistent activation of the alternative complement pathway'*

  - -Associated with C3Nef (with/without partial lipodystrophy/retinal defects)
  - -Inherited mutation of Factor H
  - -Monoclonal Gammopathies (commoner in adults)

- MPGN may present as microscopic haematuria and non-nephrotic proteinuria (35%), as nephrotic syndrome with minimally depressed renal function (35%), as a chronically progressive GN (20%) or as rapidly progressive glomerulonephritis (RPGN in 10%)
- Resolution of MPGN usually occurs after successful treatment of the associated underlying disease e.g., antiviral therapy in MPGN due to hepatitis C or B virus.
- Immunosuppressive therapy not indicated and may be deleterious in patients with hepatitis
- MPGN shows at least partial remission with treatment of other underlying conditions like myeloma or autoimmune disorders
- Patients undergoing renal transplant have high risk of recurrence from graft failure ranging from 50% in all MPGN to almost 100% in MPGN due to dense deposit disease