Chapter 9: Nephrology

Acronyms

ADH: Antidiuretic Hormone
AKI: Acute Kidney Injury
ANP: Atrial Natriuretic Peptide
BUN: Blood Urea Nitrogen
CCF: Congestive Cardiac failure
CKD: Chronic Kidney Disease
CRRT: Continuous Renal Replacement Therapy
DIC: Disseminated Intravascular Coagulopathy
ECG: Electrocardiography
FRNS: Frequently Relapsing Nephrotic Syndrome
GFR: Glomerular Filtration Rate
GN: Glomerulonephritis
HD: Haemodialysis
HSP: Henoch–Schönlein Purpura
KUB: Kidney Ureter Bladder Ultrasound
MCS: Microscopy Culture and Sensitivity
Mps: Malaria Parasites
MRDT: Malaria Rapid Diagnostic Test
NAC: N-Acetyl Cysteine
Nsaids: Non-Steroidal Anti-Inflammatory Drugs
PBF: Peripheral Blood Film
PD: Peritoneal Dialysis
PSGN: Post-Streptococcal Glomerulonephritis
RBS: Random Blood Sugar

RFT: Renal Function Test
SIADH: Syndrome Of Inappropriate Antidiuretic Hormone Release
TTP: Thrombotic Thrombocytopenic Purpura
UTI: Urinary Tract Infection

Acute Kidney Injury

Definition

Acute Kidney Injury is a syndrome characterised by rapidly declining kidney function that results in a decline in glomerular filtration rate (GFR), retention of urea and other nitrogenous waste products, and dysregulation of extracellular volume and electrolytes.

If untreated, AKI is associated with increased mortality during hospitalisation and increased risk of developing Chronic Kidney Disease (CKD). In critically ill children up to 50% have AKI.
AKI is classified into pre-renal, renal and post-renal failure. AKI is defined as any of the following

- Increase in SCr by ≥ 0.3 mg/dL (26.5 µmol/L) within 48 hours;
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days;
- Urine volume <0.5 mL/kg/hour for 6 hours.

Stages of acute injury

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	Increase ≥26 µmol/l within 48 hours or increase ≥1.5 to 1.9 x baseline SCr	<0.5mL/kg/hour for 6-12 hours
2	Increase 2-2.9 x baseline SCr	<0.5 ml/kg/hour for ≥12 hours
3	Increase ≥3 X x baseline SCr or increase 354 µmol/l or commenced on renal replacement therapy, irrespective of stage	<0.3 ml/kg/hour for ≥24 hours or anuria for ≥12 hours

KDIGO (2012)

Estimated (e)GFR can be calculated using the formula below:
Counahan-Barrat height formula for calculating eGFR in children

$$\frac{\text{Height (cm)} \times 40}{\text{Serum creatinine}} = \text{creatinine clearance}$$

Normal ranges of eGFR in children

Age	Mean eGFR (ml/min/1.73/ $m^{2)}$	Range
Birth	20	
7 days	40	25-60
1 months	50	30-70
6 months	75	40-100
12 months	115	65-160
2-12 years	125	90-165

Causes/risk factors of AKI

Types	Causes/risk factors
Pre-renal	• Most common form • Hypovolaemia (bleeding e.g. from surgery or gastrointestinal, urinary or cutaneous losses) • Reduction of effective circulation (heart failure, septic shock)
Renal – structural damage to the renal parenchyma	• **Acute Tubular Necrosis** (Epithelial cell casts): Ischemia (severe hypotension), malaria, nephrotoxic drugs, e.g. aminoglycosides, NSAIDS, amphotericin B, radio-contrast, cisplatin, acyclovir, traditional medicine etc. • Thrombotic thrombocytopenic purpura (TTP/HUS): Shiga-like toxin (E. coli), drugs, HIV, malignancy etc. • **Rapidly Progressive Glomerulonephritis**: Anti-GBM antibodies, immune- complex deposition (IgA, post-strep, lupus), pauci-immune (Granulomatosis with polyangiitis/microscopic polyangiitis) etc. • **Acute Interstitial Nephritis**: Drugs (NSAIDs, antibiotics, allopurinol, PPI), infections (CMV, strep, legionella), immune (lupus, sarcoidosis, Sjögren syndrome) • **Tubular Obstruction**: Cast nephropathy, urate crystals - Tumour lysis syndrome, calcium oxalate (Ethylene glycol), multiple myeloma (uncommon in children) e.t.c.

Post-Renal or obstructive –	• **Obstruction/hydronephrosis**: Constipation, urolithiasis, posterior urethral valves, vesicoureteral junction obstruction/reflux, schistosomiasis, etc.

Prevention/promotion

- Early health seeking behaviour
- Appropriate fluid management
- Early recognition of AKI, especially if prerenal and rapid (fluid) treatment
- Early use of inotropes to treat hypotension, especially in sepsis
- Avoid/stop all nephrotoxic drugs
- Pre-hydration in children going for major surgery or pre- chemotherapy for large tumours
- Discourage use of traditional medicine

Symptoms and signs

Paediatric AKI can present with a wide range of clinical features which include:

- Raised serum urea and creatinine
- Renal failure patient may present with clinical features of the underlying pathology e.g. Sepsis/ infection, HUS (history of bloody diarrhoea three to seven days prior to onset of oliguria), poststreptococcal glomerulonephritis (history of pharyngitis or impetigo a few weeks prior to onset of gross haematuria or oedema), shock etc.
- Oedema (nephrotic syndrome or glomerulonephritis)
- Hypertension (in glomerulonephritis)
- Rash (IgA vasculitis -Henoch Schönlein Purpura)
- Reduced urine output – Anuria or oliguria:
    - Neonates and infants – output < 1ml/kg/hour
    - Older children < 0.3 ml/kg/hour
- Polyuria- Urine output >3 ml/kg/hour, particularly with acute tubular necrosis and nephrotoxic AKI
- In pre-renal renal failure patients often present with dehydration and/or shock.
- In post renal failure, patients present with obstruction, abdominal distension and a palpable bladder
- In intra renal disease, the patient can present with oedema, signs of fluid overload, hypertension, acute weight gain, gross (or microscopic) haematuria
- Other associated symptoms may include
    - Acid base and electrolyte imbalance (especially hyperkalaemia)
    - Uraemic encephalopathy
    - Uraemic coagulopathy

- Uraemic frost

Investigations

- Malaria Rapid Diagnostic Test (MRDT)
- Random Blood sugar (RBS) test
- Urine dipstick – Haematuria, proteinuria (Glomerular disease); leukocytes and nitrites (Pyelonephritis). May be normal in prerenal AKI!
- Urine microscopy, culture and sensitivity–
- Serum creatinine and BUN
- Serum electrolytes, Calcium, Magnesium and Phosphate (CMP) + blood gas - typical biochemistry may show hyperkalaemic metabolic acidosis, hypocalcaemia, hyperphosphataemia
- Drug levels of nephrotoxic drugs (if available)
- ECG to assess signs of life-threatening hyperkalaemia (spiked T wave and/or arrythmias)
- CXR – cardiomegaly, pleural effusion, pulmonary oedema as signs of fluid overload
- Abdominal ultrasound – Kidney-ureter-bladder (KUB), size of the kidneys according to the length of the child (normal or large in AKI), and renal doppler
- FBC and differential
- Peripheral blood smear if suspecting HUS – look for schistocytes and RBC fragments
- Blood culture if febrile
- Clotting profile and Disseminated Intravascular Coagulopathy (DIC) workup if septic
- Further investigations should be guided by the underlying pathology that is suspected

Monitoring

- Monitor blood pressure and other vital signs
- Monitor daily and cumulative fluid balance:
    - Monitor input - all IV- Fluids, medication and all Oral intake
    - Catheterise to monitor urine output (at least 6 hourly)
    - Document any other losses (e.g. vomitus)
        - Daily weight

Remember to adjust the daily input and medication dose based on the patient's current weight and kidney function.

Management

Primary level

Refer all patients with oedema, hypertension, haematuria, proteinuria and oliguria/anuria to secondary level

Secondary level

Discuss to refer all patients with oedema, hypertension, haematuria, proteinuria and oliguria/anuria to tertiary facility after acute management and stabilisation of the patient

Tertiary level

- Manage all cases in conjunction with a general paediatrician, paediatric/nephrologist, urologists, dieticians.

Fluid management

- Assess and treat dehydration if the patient presents with dehydration and in shock (see management of dehydration)
- During treatment of dehydration monitor urine output and presence of extra renal losses.
- **Do not use potassium containing fluids in anuric patient.**
- Use intravenous (IV) fluids only if oral intake is not possible
- Diagnostic fluid challenge 20 ml/kg IV over 30 minutes in patients presenting with decreasing urine output history and physical findings consistent with prerenal aetiology. If urine output increases, it is likely a prerenal pathology.

Note: Fluid challenge is contraindicated if patient has signs of fluid overload and/or heart failure. Start inotropes

- **In a patient with pulmonary oedema plus oliguria/anuria, do not give fluids**
- **In a patient who is anuric with no dehydration or extra renal fluid losses**

Fluid replacement should be for insensible losses only if they require fluids for nutrition.

If patient cannot take oral fluids, then prescribe parenteral fluids with electrolyte-free solution i.e. (dextrose 5% or 10%) with caution

Insensible loses calculation:
Neonate and young infant 30-40 ml/kg/day
Older children – 25ml/kg/day (400ml/m^2/day)

- **If a patient has normal hydration and oliguria:**

- Give oral fluids to replace insensible water loss plus urine output of previous 24 hours.

- **If the patient is dehydrated and has on going extra-renal fluid losses:**

Replace fluid according to losses with an appropriate fluid solution similar to the losses e.g.

- Diarrhoea losses give ½ strength Darrow's or Dextrose 5% IV or oral rehydration solution (ORS)
- Vomiting/gastric fluid losses give normal saline (0.9%)/dextrose 5%.

- **If the patient is normally hydrated with normal urine output**:
  - Give normal intake

- **If the patient is in shock**: (see management of shock)
- **If the patient has polyuria with urine output >4ml/kg/hr:**
  - Commonly seen in patients who are recovering (diuretic phase) from acute tubular necrosis (ATN)
  - Give fluid and electrolyte losses with ½ strength Darrow's / Dextrose 5% IV.

Nutritional support

- High-energy diet (infants 120 kcal/kg/d, older children 150 kcal/kg/d), supplement via nasogastric
- tube is needed
- Encourage breast milk for infants, if not enough add formula feeds
- Daily requirements
  - Protein – 1g/kg/day maximum
  - Carbohydrate - 2-3 g/kg/day
  - Fats – 2g/kg/day
- Restrict salt intake
- Do not give potassium or phosphorus containing fluids to patients with oligo-anuric AKI unless they have significant hypokalaemia or hypophosphatemia
- Restrict protein intake when serum urea > 25mmol/L (450mg/dL)

Electrolyte and acid base management

- Replace electrolyte deficits according to monitored serum levels of electrolytes
- Note that once correcting acidosis, calcium levels are affected
- Manage hyperkalaemia (see management of hyperkalaemia)
- Manage Metabolic acidosis (serum pH ≤ 7.1)
- IV fluid therapy with Ringers Lactate instead of Normal Saline
- Give sodium bicarbonate 4.2% IV, 4mL/kg administered over 2-4 hours. Do not mix calcium and sodium bicarbonate containing solutions.

Manage hypertension

- Four limb blood pressure (BP) measurement

- If BP has systolic or diastolic measurements ≥95th percentile for gender and age, patient has hypertension and must be managed– see management of hypertension in children

Manage any concurrent infections and avoid nephrotoxic drugs

- Antibiotic treatment if poststreptococcal GN is suspected
- Adjustment of drug dosing in renal failure
- Discuss with paediatrician/nephrologist and/or pharmacist concerning the possible nephrotoxic drugs
- Stop the offending drug or adjust the drug dose to renal friendly doses if the benefit outweighs the risk

Avoid nephrotoxic or renally excreted medicines e.g. NSAIDS, aminoglycosides, vancomycin, cough and cold mixtures, ratio-contrast drugs

Manage uraemic convulsions

- (see management of seizures)
- Refer the patient for urgent dialysis
- Exclude other treatable causes of convulsions e.g. hypoglycaemia, hyper- or hyponatraemia, hypocalcaemia, hypertension etc.

Manage and treat pulmonary oedema, fluid overload and hypertension

- Do not give fluids to anuric patients with pulmonary oedema
- Refer for urgent dialysis
- Provide respiratory support as soon as possible.
  - Give 100% oxygen, 2-3L/minute by nasal prongs escalate to face mask if needed for comfort
  - CPAP
  - Intubate and initiate positive pressure ventilation as soon as possible where indicated
- Furosemide IV, 2 - 5mg/kg given over 5 minutes (maximum daily dose is 8mg/kg/24 hours)
  - Closely monitor electrolytes, especially in high doses
  - Care must be taken, as furosemide can also deteriorate the renal function
  - If oliguria and/or creatine worsen – think about renal replacement therapy
- Morphine IV, 0.1mg/kg 4 hourly (with caution and close monitoring)

Renal replacement therapy (RRT)

- Think about RRT early as some conditions are rapidly progressing (e.g. HUS)
- The choice of RRT depends on the clinical status of the patient, the expertise of

the clinician and the availability of resources.

- Haemodialysis (HD)
- Peritoneal dialysis (PD)
- Continuous RRT (CRRT)

Indications for RRT: AEIOU

- Acidosis: Not responsive to medical management
- Electrolytes: Refractory hyperkalaemia (serum or plasma potassium >6.5 mEq/L) unresponsive to non-dialytic therapy (See "Management of hyperkalaemia in children".)
- Intoxications: Drug toxicity (not for all drugs, please check if appropriate)
- Overload fluid: Refractory to diuretics
- Uraemic complications: Pericarditis, encephalopathy

Involve palliative care team from the onset if considering RRT!!!

Follow up

Follow up in PEN-Plus clinic in 1 month

Chronic Kidney Disease (CKD)

Definition

This is a clinical condition characterised by progressive, irreversible loss of kidney function due to abnormalities of the kidney structure or function (measured by proteinuria and/or reduction of estimated GFR) present for more than 3 months.

The diagnosis requires fulfilment of one of the two criteria, clearly documented or inferred for more than 3 months: either GFR <60 mL/min/1.73m^2 or presence of markers of kidney damage including albuminuria (proteinuria)

Staging of chronic kidney disease (KDQOI)

Stage	Estimated GFR (mL/min/1.73 m^2)	Features
1	≥90	Renal parenchymal disease present
2	60-89	Usually asymptomatic – biochemical abnormalities present
3	30-59	Biochemical abnormalities and poor growth, poor appetite
4	15-29	
5	<15 (ESRF)	End stage renal failure.

Risk factors/causes

- Congenital renal abnormalities (e.g. obstructive uropathy, PUV, polycystic kidney disease) – Account for 60% of Paediatric CKD
- History of acute kidney injury
- Medical conditions that can affect kidney function
- Nephrotic syndrome
- Vasculitides / Autoimmune disorders – e.g. Immunoglobin A vasculitis (previously called HSP), Takayasu arteritis
- Infections and infestations – e.g. HIV, malaria, syphilis, schistosomiasis, TB
- Genetic disorders – e.g. sickle cell disease, polycystic kidney disease
- Diabetes
- Cardiovascular disease - high blood pressure
- Family history of kidney disease
- Exposure to nephrotoxins (consider herbal remedies)

All patients presenting with risk factors must be screened for CKD

Promotion/prevention

- Early health seeking behaviour
- Education and advocacy
- Early screening and detection in patients at high risk of CKD
- Scheduled follow up of at-risk patients, especially after AKI, with congenital abnormalities
- Appropriate fluid management
- Avoid/stop all nephrotoxic drugs
    - stop early if cannot be avoided
- Antibiotic prophylaxis and early operation, if possible, for congenital UT abnormalities
- Discourage use of traditional medicine
- Confirm drug doses for children based on their weight and adjust accordingly

Signs and symptoms

<u>Key points in history</u>

- Thorough history of previous renal diagnoses. Children can present with acute on chronic renal failure during episodes of an acute illness.
- Antenatal history (polyhydramnios?), postnatal history, family history and possible exposure to traditional or complimentary herbal medicines and nephrotoxic drugs
- Hypertension
- Recurrent UTI
- Early UTI in infancy – needs screening for UT abnormalities
- Incomplete voiding (abnormal stream)
- Dysuria
- Haematuria
- Anuria or oliguria
- Chronic anaemia, chronic constipation, polyuria, polydipsia.

<u>Key points on examination</u>

- Thorough physical examination which must include dysmorphic features (especially looking at the ears, genitourinary system, back and spine deformities and the skin)
- Anthropometric measurement and assessment
- Poor growth – failure to thrive (FTT), severe stunting and poor weight gain
- 4 limb blood pressure if systolic or diastolic blood pressure is ≥95% percentile for gender and age, the child has hypertension. Refer to management of hypertension in children
- General body swelling
- Flank abdominal pain

- Signs and symptoms of salt wasting in children with renal tubular disorders or bilateral renal dysplasia.
    - These patients lose the ability to concentrate urine. The patient will present with dehydration and metabolic acidosis
- Bone pain and skeletal deformities e.g. signs suggestive of rickets or osteomalacia
- Signs of fluid overload
    - Oedema, hypertension, heart failure and pulmonary oedema
- Signs and symptoms of raised urea
    - Nausea, vomiting pruritus, brownish skin pigmentation, uraemic frost
- Bleeding tendency
- Convulsions due to hyponatraemia, hypernatremia, hypocalcaemia, uraemia or hypertension

Investigations

- Calculated estimated Glomerular Filtration Rate (eGFR) assesses kidney function and albuminuria/ proteinuria assesses kidney injury
- Urine dipstick, urine Microscopy, culture and sensitivity
- FBC
- Serum urea and creatinine
- Serum electrolyte
    - Hyperkalaemia, hyperchloremia and decreased bicarbonate are common in CKD
    - Hypocalcaemia, hyperphosphatemia and increased ALP are common manifestation of CKD
- 25-hydroxyvitamin D
- Parathyroid hormone (PTH)
- Liver function test
- Imaging:
    - CXR- pulmonary oedema?
    - Cardiac echo
    - Abdominal USS, KUB and renal artery Doppler
    - Renal USS can reveal obstruction.
    - Small shrunken kidneys are suggestive of CKD
    - Abdominal CT angiography in cases presenting with hypertension
    - No biopsy is indicated in cases of CKD

Management

Primary level

- Manage any emergency signs and refer every patient to secondary level when CKD is suspected

Secondary level

- Stabilise the patient if acutely unwell with supportive therapy as indicated

<u>General and supportive care</u>

- Identify and treat the underlying cause of CKD
- Avoid further kidney damage – treat hypoperfusion early, detect and treat infections early, strict BP control
- Start oxygen support if indicated
- Do not give blood unless the child has symptomatic or severe anaemia <7g/dL
- Monitor BP and other vital signs
- Daily weight
- Monitor input
- Monitor output
  - Document any losses
  - Monitor Urine output
    - Catheterize only if indicated - catheter placement may not always be needed (infection risk)

<u>Initiate management of complications</u>

- Manage pulmonary oedema (see management of pulmonary oedema)
- Manage hypertension (see management of hypertension)
- Manage UTI with antibiotics
- Manage diabetes complications (see management of diabetes)
  - Discuss then refer patient to tertiary level

Tertiary level

- Stabilise the patients with supportive therapy
  - Start oxygen support
  - Do not give blood unless the child has symptomatic severe anaemia
  - Catheterise and monitor urine output
- Identify and treat underlying cause

Fluid Management

- Assess and treat dehydration (see management of dehydration)
  - During treatment of dehydration consider urine output and presence of extra renal losses. Do not use potassium containing fluids in

anuric patients
    - Use intravenous (IV) fluids only if oral intake is not possible (refer to the section on AKI)
- **In a patient with pulmonary oedema plus oliguria/anuria:**
    - DO NOT GIVE FLUIDS!!
- **In a patient who is anuric with no dehydration or extra renal fluid losses**:
    - Fluid replacement should be for insensible losses only (see AKI section for calculation)
    - If the patient cannot take oral fluids, then prescribe a parenteral fluid with electrolyte-free solution i.e. (dextrose 5% or 10%)

- **If a patient has oliguria, oedema and hypertension**
    - Give oral fluids to replace insensible water loss plus urine output of previous 24 hours plus extra-renal losses
    - When the patient improves calculate the losses within the previous 12 hours and replace for the next 12 hours to give a total of 100% fluid loss replacement

- **If the patient is dehydrated and has on going extra-renal fluid losses:**
    - Replace fluid according to losses with appropriate fluid solution similar to the losses e.g.
    - Diarrhoea losses give ½ strength Darrow's or dextrose 5% IV or oral rehydration solution (ORS)
    - Vomiting/gastric fluid losses give normal saline (0.9%)/dextrose 5%.

- **If the patient is normally hydrated with normal urine output:**
    - Give normal intake
- **If the patient is in shock:** (see management of shock)
    - Manage Pulmonary Oedema (see management of pulmonary oedema)
    - Manage hypertension (see management of hypertension in children)

<u>Manage Chronic Metabolic Acidosis and Electrolyte Abnormalities</u>

- If serum bicarbonate is <18mmol/L give sodium bicarbonate, orally, 1 mmol/kg/dose 2-3 doses per day after meals.
    - Adjust according to response. The intravenous formulation can be given orally.
- If patient has severe metabolic acidosis with serum pH ≤ 7.1
    - Give sodium bicarbonate 4.2% IV 4mL/kg administered over 2-4 hours. *Do not mix calcium and sodium bicarbonate containing solutions!*
- Replace electrolyte deficit according to monitored serum levels of electrolytes
- Manage hyperkalaemia (see management of hyperkalaemia)

Manage and treat anaemia

- Give iron supplements which include iron, folic acid or vitamin B12 and ensure that there are adequate iron stores by measuring ferritin, transferring saturation and total iron binding capacity regularly
- If patient has persistent Hb <8g/dL despite correction of possible deficiencies of iron, folic, acid or vitamin B12, start recombinant human erythropoietin (rHEPO).

  - Give EPO, SC, 75units/kg/week in divided doses 2–3 times per week.
  - Increase dose gradually whilst monitoring Hb levels every 4 weeks. Aim to increase Hb to 10-12g/dL .
    - If the Hb level is increasing with the initial dose, do not change dose.
      - If Hb level increases > 12 g/dL, stop treatment for one week. Thereafter continue with 25% less than previous dose per week.
    - If Hb level increase is not satisfactory adjust dose until target haemoglobin level of 12 g/ dL is reached, then maintain the same EPO dose.
      - Increase by 25% at 4-week intervals until maximum dose of 300units/kg/week is reached.

- Avoid unnecessary transfusions due to risk of developing antibodies in patients who may be potential candidate for renal transplant
- For patients with symptomatic anaemia and Hb < 7g/dL give packed red blood cells 10ml/kg administered over 6 hours

<u>Manage Infections & Review Prescribed Medications</u>

- Manage any concurrent infections and avoid nephrotoxic drugs
- Manage UTI with antibiotics
- Adjustment of drug dosing in renal failure
- Discuss with pharmacist concerning the possible nephrotoxic drugs
- Stop the offending drug or adjust the drug dose to renal friendly doses if the benefit outweighs the risk

Avoid nephrotoxic or renal excreted medicines e.g. NSAIDS, aminoglycosides, Vancomycin, cough and cold mixtures, radio-contrast drugs

Manage diabetes complications (see management of diabetes)

Provide Nutritional Support

- Involve the dietician as soon as possible (e.g. salt restriction, high calorie, high protein, low potassium diet)
- High-energy diet (aiming for 120%), supplement via nasogastric tube is needed. Encourage breast milk for infants - if not enough, add formula feeds
- Do not restrict protein intake in all patients with CKD
- If potassium is >5.5 mmol/L, reduce potassium intake.
  - Restrict fruit juices, dried fruit, all citrus fruits, bananas, guavas and tomatoes. These foods have high potassium content.
  - All vegetables should either be soaked for 24 hours before cooking or water should be decanted twice during cooking.
- If phosphate is > 1.8 mmol/L with a GFR <70 ml/min/1.73m2 reduce phosphate intake
- Reduce salt intake - no salt should be added during food preparation or during meals.
  - Do not allow salt preserved foods. No salt intake in all patients with hypertension and oedema.
- **Note:** Do not restrict salt intake in patients with salt-losing nephropathies.

Provide Vitamin and Mineral Supplements

- Give multivitamin orally 5 ml/day - Choose formulations that have pyridoxine, other B vitamins, Vitamin C 30mg and vitamin D 400IU.
- Give folic acid, orally, 5mg/day.
- For management of hyperphosphatemia/ osteodystrophy and hyperparathyroidism:
  - Restrict foods rich in phosphate
  - Give calcium carbonate orally 1-4 chewable tablets 8 hourly with meals (1 tablet = 1.68g elemental calcium)
  - Give Alfacalcidiol oral 0.25mcg daily
  - Discuss with seniors/paediatrician or specialist if available.
    - In patients with serum calcium < 2.2mmol/L start alfacalcidiol 0.25mcg twice weekly and increase dose as instructed by specialist or senior medical personnel to maintain normal calcium range.
    - If serum phosphate >2.5 mmol/L treat hyperphosphatemia first to decrease to <1.8mmol/L before starting alfacalcidiol to avoid metastatic calcification

Manage dyslipidaemia in CKD

- Dyslipidaemia may contribute to the progression of chronic kidney disease,

particularly in children with nephrotic syndrome.
- Hypertriglyceridemia and abnormal apolipoprotein metabolism are feature of CRF.
- Dietary intervention includes reducing foods with saturated fats and cholesterol
- For children > 8 years with persistent total cholesterol levels > 7 mmol/L, give statins - HMGCoA reductase inhibitors e.g. simvastatin orally, 10 mg (maximum dose of 20 mg) at night.
- Discuss with seniors before initiation.

Provide Reno-Protective Treatment
- All children with persistent nephrotic range proteinuria and GFR > 30 mL/minute give ACE inhibitor e.g. enalapril oral 0.1 mg/kg/dose, once daily.
  - Increase dose to 0.5 mg/kg/day, as a single dose or two divided doses.
  - Monitor for adverse effects which include hyperkalaemia (increased risk when potassium sparing diuretic is used simultaneously) and acute renal failure (increased risk in children with impaired renal function or volume depletion) and cough (often main reason why patients would stop taking the drug)
  - ACE inhibitor may worsen metabolic acidosis and cause a decline in renal function while reducing proteinuria. Therefore, monitor serum urea and electrolytes i.e. serum potassium, bicarbonate, and renal function within 7 days of starting the drugs.
  - If serum creatinine has doubled, check hydration status, stop diuretics and halve the dose of ACE inhibitors
  - If renal function does not improve, or hyperkalaemia > 5.5 mmol/L persists, stop ACE inhibitor treatment.

Other Management Considerations
- Consult the urology (surgical) team if the patient has confirmed obstructive uropathy
- Consider haemodialysis where the patient meet criteria and services are available (see indications
- for dialysis)
- Start palliative care support soon after diagnosis of CKD
- Ensure that the child is fully vaccinated and provide catch-up immunisations as appropriate

Follow up
- Follow up in PEN-Plus clinic regularly

Nephrotic Syndrome

Definition

Nephrotic syndrome is a clinical syndrome associated with heavy proteinuria due to increased permeability of the glomerular basement membrane.
The diagnostic criteria include the following:

- Oedema
- Proteinuria (at least 3+ on urine dipstick)
- Hypoalbuminaemia (<30g/L)
- Hyperlipidaemia

Causes /risk factors

- Primary
  - Idiopathic (minimal change; focal segmental glomerulonephritis (GN) - most frequent, usually responds to corticosteroids)
- Secondary
  - Infections (e.g. post infectious glomerulonephritis, malaria, HIV, TB, hepatitis B & C, schistosomiasis, syphilis)
  - Drugs (NSAIDs)
  - Autoimmune disease (Systemic Lupus Erythematosus)
  - Mechanical (obstructive neuropathy)
  - Malignancy (lymphoma)
- Congenital/infantile (present at birth or in children less than 1 year)
  - Immune disorders (infantile systemic lupus erythematosus)
  - Infective (TORCH, Hepatitis B)

Prevention/promotion

- Vaccination against common medical conditions associated with NS e.g. malaria, Hepatitis B, *streptococcus pneumonia* infections etc.
- Health education and advocacy
- Early identification
- Averting complications (e.g. preventing infections of encapsulated organisms, thromboembolic events, malnutrition and progress to chronic kidney disease)

Symptoms and signs

- Oedema
  - Often starts under the chin and around the eyes and may become generalised (anasarca, genitals, ascites and pleural oedema)
  - Dependent on position and activity of the child – upon waking usually

periorbital or facial oedema, decreases over the day while anasarca and pretibial oedema increase

Differential Diagnosis

- Other causes of oedema e.g.
  - Malnutrition (bilateral pitting oedema that does not vary with position), cardiac failure, liver cirrhosis, allergies, severe anaemia
- Other renal causes of oedema – e.g. glomerulonephritis, renal failure

Investigations

- Blood pressure (usually normal)
- Urine dipstick – ≥ +3 proteinuria, trace to +1 haematuria
- Spot random urine sample for protein: creatinine ratio (> 0.2g/mmol)
- Urine microscopy – hyaline and lipid casts are seen occasionally, red and white blood cell casts seen
- FBC
- HIV, malaria, syphilis, CMV antibody, hepatitis B and C serology to exclude secondary causes of NS
- Stool microscopy for schistosomiasis
- Urea and creatinine – often within normal range
- Electrolytes
- Liver Function Tests
- Raised cholesterol levels
- Hypoalbuminaemia (Serum albumin < 3 g/dL)
- Complement levels
- TB workup
  - Mantoux
  - CXR: to Rule out TB

Note: Other more advanced investigations including kidney biopsy should be taken in consultation with a paediatric nephrologist and histopathologist.
All patients with clinical signs of steroid resistant nephrotic syndrome should have a renal biopsy.
Please refer to the Nephrologist.

Management

- Hospitalise for initial therapy
- General supportive measures
  - Monitor fluid balance. Do not fluid restrict
  - Monitor urine output

- Daily weight and adjust the medication dosages according to current weight
- Assess hydration status
- Suspect hypovolaemia if patient has hypotension, small pulse volume and cold extremities
- Encourage ambulation
- Replace on going renal losses (See management of dehydration in children).

- Nutritional support
  - Do not restrict oral fluid intake
  - Restrict salt intake in all patients
  - Ensure normal calorie and protein intake (for patients with normal renal function)

Primary level

Refer all patients with nephrotic range proteinuria (≥3+) ± oedema to secondary level

Secondary level

Supportive management

- Fluid balance – daily weight, urine output monitoring, BP monitoring
- Do not restrict oral fluids (risk of thrombosis due to hyper coagulopathy)
- Diet – salt and fat diet restriction, involve a dietician if available
- Encourage ambulation to prevent thromboembolic events
- Treat infections as soon as they appear (NS patients are more prone to infection. Also, infections are often a trigger for relapses)

Pharmacological Treatment

- Treat intercurrent infection before starting steroids
- Exclude active tuberculosis
- Start steroids:
  - Prednisolone 2mg/kg/day with maximum dose 60mg/day for 4 weeks
  - Review after 4 weeks. Check urine dipstick:
    - If in complete remission: steroid sensitive nephrotic syndrome
    - Wean prednisolone 1.5mg/kg on alternate days for 4 weeks

    If not yet in complete remission at 4 weeks
    - Continue prednisone up to 6 weeks
    - if goes into remission: **steroid sensitive late responder.** Wean
    - prednisolone 1.5mg/kg alternate days for 6 weeks.
    - If not in remission after 6 weeks of prednisolone; **steroid resistant nephrotic syndrome.** Wean prednisolone as above

For all patients taking steroids, monitor, check and manage complications of steroids (e.g. eye cataracts, adrenal insufficiency, reflux, poor growth, Cushing's syndrome etc.)

prescribe calcium and vitamin D supplements for all children on steroids for nephrotic syndrome

- **Do not use furosemide unless a child has signs of pulmonary oedema or respiratory distress**

(see pulmonary oedema treatment guidelines)

  - Treat with the lowest possible dose, e.g. 0.5 mg/kg BD)
  - Children with nephrotic syndrome even with gross oedema, may be intravascularly depleted and frusemide can result in acute kidney injury

- Look for and initiate management of complications and refer for tertiary level care. Complications include the following:
  - Thrombotic events (e.g. stroke, DVT)
  - Spontaneous bacterial peritonitis
  - Hypovolaemic shock
  - Electrolyte imbalances

Refer if gaining weight or has oliguria/anuria or is not in remission at 6 weeks (i.e. urine dipstick with protein trace for ≥3 days in a row)

Tertiary level

- Management as above
- If critically low albumin with oedema causing symptoms:
  - IV albumin 0.5-1g/kg slowly over 4 hours with frusemide half way. (please ensure the patient is passing urine)
  - If albumin not available consider using FFPs 15mL/kg over 4 hours
- For steroid dependant or frequently relapsing nephrotic syndrome
  - Low-dose prednisolone
    - 0.5mg/kg alternate days (maximum 20mg alternate daily)
    - 0.25mg/kg daily (maximum 10mg)
  - Cyclophosphamide
    - 2mg/kg/day for 12 weeks
    - 3mg/kg/day for 8 weeks

    Note: maximum dose 150mg and follow up FBC 14 days after starting treatment then monthly
  - Other steroid sparing agents: cyclosporine, MMF, rituximab

- For steroid-resistant nephrotic syndrome
  - RAAS inhibitors to decrease proteinuria
  - Calcineurin inhibitors if available: cyclosporine or tacrolimus

Follow up

- Follow up in PEN-Plus clinic. During the initial part of treatment, follow up has to be frequent to monitor response.

Definitions:

Term	Definition
Nephrotic-range proteinuria	Urinary protein creatinine ratio (UPCR) ≥ 200 mg/mmol (2 mg/mg) in a spot urine, or proteinuria ≥1000 mg/m^2 per day in a 24-h urine sample corresponding to 3 + (300-1000 mg/dL) or 4+(≥1000 mg/ dL) by urine dipstick
Nephrotic syndrome	Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30g/L) or enema when serum albumin is not available
Complete remission	UPCR (based on first morning void or 24h urine sample) ≤ 20mg/mmol (0.2 mg/mg) or < 100 mg/m^2 per day, respectively, or negative or trace dipstick on three or more consecutive days
Partial remission	UPCR (based on first morning void or 24 h urine sample) > 20 but <200 mg/mmol (>0.2 mg/mg but <2 mg/mg) and serum albumin ≥ 30 g/L
Steroid-sensitive nephrotic syndrome (SSNS)	Complete remission within 4 weeks of PDN at standard dose (60 mg/m^2 / day or 2 mg/ kg/day, maximum 60 mg/day)
Steroid-resistant nephrotic syndrome (SRNS)	Lack of complete remission within 4 weeks of treatment with PDN at standard dose
Confirmation period	Time period between 4 and 6 weeks from PDN initiation during which responses to further oral PDN and/or pulses of IV MPDN and RAASi are ascertained in patients achieving only partial remission at 4 weeks. A patient not achieving complete remission by 6 weeks, although partial remission was

	achieved at 4 weeks, is defined as SRNS
SSNS late responder	A patient achieving complete remission during the confirmation period (i.e. between 4 and 6 weeks of PDN therapy) for new onset NS
Relapse	Urine dipstick ≥ 3 + (≥ 300 mg/dl) or UPCR ≥ 200 mg/mmol (≥2 mg/mg) on a spot urine sample on 3 consecutive days, with or without reappearance of oedema in a child who had previously achieved complete remission
Infrequently relapsing nephrotic syndrome	<2 relapses in the 6 months following remission of the initial episode or fewer than 3 relapses in any subsequent 12-month period
Frequently relapsing nephrotic syndrome (FRNS)	≥2 relapses in the first 6-months following remission of the initial episode or ≥ 3 relapses in any 12 months
Steroid-dependent nephrotic syndrome (SDNS)	A patient with SSNS who experiences 2 consecutive relapses during recommended PDN therapy for first presentation or relapse or within 14 days of its discontinuation
Steroid toxicity	New or worsening obesity/overweight, sustained hypertension, hyperglycaemia, behavioural/psychiatric disorders, sleep disruption Impaired statural growth (height velocity < 25th percentile and/or height <3rd percentile) in a child with normal growth before start of steroid treatment Cushingoid features, striae rubrae/distensae, glaucoma, ocular cataract, bone pain, avascular necrosis
Sustained remission	No relapses over 12 months with or without therapy
SSNS controlled on therapy	Infrequently relapsing NS or sustained remission while on immunosuppression in the absence of significant drug-related toxicity
SSNS not controlled on therapy	Either frequently relapsing NS despite immunosuppression or significant drug- related toxicity while on immunosuppression
Secondary steroid resistance	SSNS patient who at a subsequent relapse does not achieve complete remission within 4 weeks of PDN at standard dose

Complicated relapse	A relapse requiring hospitalization due to one or more of the following: severe oedema, symptomatic hypovolemia or AKI requiring IV albumin infusions, thrombosis, or severe infections (e.g., sepsis, peritonitis, pneumonia, cellulitis)

Glomerulonephritis/Nephritic Syndrome

Definition

This is a clinical manifestation of glomerular injury due to massive inflammation, characterised by haematuria, hypertension and oedema (can also have proteinuria). It can lead to impaired kidney function.

Causes

Primary glomerulonephritis (GN)

Isolated kidney disease

- Membranoproliferative glomerulonephritis
- Immunoglobulin A (IgA) nephropathy
- Anti-glomerular basement membrane (GBM) disease
- Idiopathic crescentic GN

Secondary GN

Systemic disease

- Post-streptococcal GN (most common cause)
- Other postinfectious GN (Staphylococcus aureus, E.coli, Mycoplasma, Salmonella typhi, EBV,
- Parvo B19, Varicella, Hepatitis B, Schistosomiasis, Malaria)
- IgA vasculitis (Henoch-Schönlein purpura)
- Systemic lupus erythematosus nephritis
- ANCA-associated vasculitis
- Nephritis associated with infective endocarditis
- Goodpasture syndrome

Risk factors

- Upper respiratory tract infection/pharyngitis (Group A streptococcal infection - GAS); common between 2-6 years of age
- Bacterial infection (streptococcal and staphylococcal) e.g. pyoderma, impetigo, abscesses, atypical pneumonia etc.
- Viruses e.g. Hepatitis B infection
- Vasculitis disorders e.g. autoimmune disorders and others
- Alport Syndrome

Promotion/prevention

- Early health seeking behaviour
- Early detection and treatment of sore throat and skin infections including scabies

- Adhere to the national EPI programme for vaccine

Signs and Symptoms

- Sudden onset of haematuria (microscopic or gross) ±proteinuria
- Oliguria
- Oedema (fluid retention) with facial swelling dyspnoea
- Abdominal pain
- Rapid weight gain
- Hypertension which can cause headache, seizures and visual impairment
- Rash secondary to HSP, IgA nephropathy, infected scabies

Investigations

- Four limb blood pressure if systolic and diastolic blood pressure is >95th percentile for age and gender, the patient has hypertension.
- Urine appearance – smoky, brown or bloody.
- Urine dipstick – +1 to +3 haematuria ± trace to +2 proteinuria
- Urine microscopy – including red cells that are dysmorphic with or without red and granular casts
- Urine culture
- Decreased C3 and normal C4 complement levels
- Anti-streptolysin O (ASO) anti-DNAse B titre if available. ASO is usually positive in the absence of prior antibiotic treatment. It is often negative in preceding skin infections.
- Urea and creatinine – mildly elevated in the acute phase of the disease
- Electrolytes – hyponatraemia, hyperchloremic hyperkaliaemic metabolic acidosis is common
- FBC – anaemia with normal platelet count
- Blood cultures
- Hepatitis B virus screening
- Abdominal USS and KUB plus renal artery doppler
- Cardiac echocardiography if hypertensive or signs of fluid overload
- ESR
- Kidney biopsy

Differential Diagnosis

- Other causes of oedema e.g. malnutrition, cardiac failure, liver cirrhosis, allergies, severe anaemia
- Other renal causes of oedema – e.g. nephrotic syndrome, renal failure
- Other causes of hypertension e.g. coarctation of aorta, aortic stenosis, brain tumours, Takayasu arteritis

- Malignancy e.g. Wilms' tumour
- Drugs (rifampicin, ibuprofen)
- Haemoglobinurias and myoglobinuria

Management

Primary level

- Manage emergencies e.g. manage ABCDE, administer frusemide 1-2 mg/kg stat dose if fluid overload
- Manage seizures according to the seizure protocol
- Refer all patients presenting with oedema, hypertension and haematuria to secondary level

Secondary Level

- Manage ABCDE
- Manage seizures according to the seizure protocol
- Manage pulmonary oedema and hypertension
  - Hypertension develops acutely due to fluid overload and normalises after treatment
  - Measure BP regularly – at least 6hourly but preferred to be in HDU if hypertensive for more frequent monitoring
  - Give Furosemide 1-2 mg/kg
  - (see pulmonary oedema and hypertension management)
- Bed rest for patients with severe hypertension or pulmonary oedema (semi-seated position)
- Fluid balance
  - Daily weight, urine output monitoring, BP monitoring
  - Fluid management according to fluid status
  - Strict fluid intake
  - Avoid using IV fluids - If IV fluids need to be administered, then a potassium-free fluid is ideal
- Diet
  - Restrict salt intake in all patients presenting with GN
  - Restrict potassium intake until results of potassium are available
- Antibiotic therapy (post-streptococcal glomerulonephritis)
  - Amoxycillin 15mg/kg/dose 8hourly (maximum 500mg/dose) for 10 days
    OR
  - Benzylpenicillin 50,000 IU/kg IV 6 hourly for 10 days
    OR
  - Benzathine penicillin STAT dose
    - 600,000 IU if ≤ 25kg or 1,200,000 IU if >25kg
    OR
  - Alternative drugs if there is history of penicillin sensitivity is oral

erythromycin 10 mg/kg/ dose 6 hourly for 10 days

- All patients with complications (refractory seizures, hypertensive encephalopathy), those not improving after antibiotic and supportive treatment must be discussed and referred to tertiary hospital Involve palliative care and psychosocial support

Tertiary level

- Manage as above
- Supportive therapy
- Manage pulmonary oedema (see pulmonary oedema management)
- Manage hypertension (see hypertension management)
- Manage electrolyte and acid base derangements
- Dialysis if indicated, should be commenced as soon as possible (see indications for dialysis)
- Involve the palliative care team if the disease becomes chronic or requires dialysis
- In rapidly progressive GN (rapid decline in GFR of at least 50% over a few days to 3 months)
  - high dose steroids
    - Methylprednisolone 10mg/kg for 3 days then 2mg/kg prednisone and wean over 4 weeks if not available 2mg/kg prednisolone for 5 days and wean
    - Cyclophosphamide IV

Management of the patient should be in conjunction with a general paediatrician, paediatric nephrologist if available and infectious disease specialist

Follow up

- Follow up in PEN-Plus clinic
- Most cases of acute GN are due to PSGN- symptoms resolve within one or two weeks of presentation. Adapt antihypertensive drugs. These are usually only needed initially
- If unsure of diagnosis of PSGN, then do a kidney biopsy (nephrologist consultation)

Haemolytic Uraemic Syndrome (HUS)

Definition

It is a clinical syndrome of thrombotic microangiopathy characterised by the following triad:

- Micro-angiopathic haemolytic anaemia (fragmented erythrocytes)
- Thrombocytopenia
- Acute Kidney Injury (AKI)

Subtypes

- Shiga toxin-producing Escherichia Coli HUS (STEC-HUS)- 90%
- Non STEC-HUS

Risk factors/causes

Acquired Infectious

- STEC – usually 5-10 days after onset of diarrhoea
- Shigella
- *Streptococcus pneumoniae*
- HIV Infection
- Malaria
- H1N1 influenza A
- Parvovirus B19

Acquired non-infectious

- Autoantibodies to complement factors
- Drug toxicity, particularly in patients with cancer or solid organ transplant recipients
- Pregnancy
- Autoimmune disorders e.g. SLE

Hereditary

- Complement gene mutations in children
- Inborn errors of cobalamin C metabolism
- Diacylglycerol kinase epsilon (DGKE) gene mutations

Promotion/prevention

- Promote hygiene and sanitation
- Vaccination
- Early recognition and treatment

Signs and symptoms

- Petechiae and easy bruising
- Fever
- Abdominal pain
- Bloody diarrhoea
- Pallor
- Hypertension – common
- Oliguria or anuria
- CNS manifestations – reduced level of consciousness or seizures
- Severe AKI in ½ of the HUS cases

Differential diagnosis

- DIC – Disseminated Intravascular Coagulopathy
- TTP – Thrombotic Thrombocytopenic Purpura
- Systemic vasculitis
- Immunoglobin A vasculitis

Investigations

- Urine dipstick and urinalysis
- Full blood count – Hb usually less than 8g/dL
- Peripheral Blood Film
    - Schistocytes (RBC fragmentation) in up to 10% of erythrocytes
- Findings of haemolysis: high indirect bilirubin concentration, reduced serum haptoglobin, raised LDH
- HIV test
- Urea and creatinine (raised)
- Electrolytes
- Stool microscopy, culture and sensitivity
- Stool shiga toxin ELISA
- Blood culture
- Additional laboratory tests may be needed in case-by-case basis to exclude other possible diagnoses that present in a similar manner (differential diagnosis):
    - Coagulation profile
    - Autoimmune work-up (Coombs test, ANA, Anti-dsDNA, ANCA)

Management

Primary level

- Manage emergency conditions – ABCDE
- Refer to next level of care

Secondary level

- Manage emergency conditions – ABCDE
- Transfuse blood in anaemic patients with haemoglobin level below 6 or haematocrit <18 percent (see Malawi Blood Transfusion Guidelines)
- Refer urgently to next level of care

Tertiary level

- **Manage emergency conditions –** ABCDE
- **Transfuse blood transfusion** in anaemic patients' haemoglobin level < 6g/dL or haematocrit <18% (see Malawi Blood Transfusion Guidelines) – aim for an HB of 8-9 g/dL (not higher due to risk of fluid overload)
- **Transfuse Platelet** for patients who have low platelet count with significant active clinical bleeding
- **Supportive therapy**
  - Manage pulmonary oedema (see pulmonary oedema management)
  - Manage hypertension (see hypertension management)
  - Manage fluid and electrolyte to maintain adequate intravascular volume and correct/avoid electrolyte imbalances (see management of electrolyte imbalances)
  - Manage seizures
- **Stop** nephrotoxic drugs or those drugs associated with HUS e.g. gentamicin, vancomycin
  - A trial of frusemide in severe fluid overload can be performed, but stop diuretics if no effect
- **Start** dialysis therapy (see indication for AKI)
- **Provide** adequate nutrition

Follow up

- Follow up the patient in PEN-Plus clinic as appropriate

Electrolyte Imbalances

Hyperkalaemia

Definition

Serum or plasma potassium greater than 5.5 mmol/L

- Potassium levels > 7 mmol/L is an emergency requiring immediate treatment

Risk factors/causes

Excessive potassium intake:

- IV Fluids with high potassium content
- Massive blood transfusion
- Parenteral nutrition e.g. TPN
- IV medications with high potassium content e.g. NSAIDS
- Rarely diet intake e.g. bananas

Transcellular movement of intracellular potassium into the extracellular space

- Cellular injury: Rhabdomyolysis, burns, trauma, extreme exercise (exertional heat illness), tumour lysis syndrome, gut necrosis and severe haemolytic disorders.
- Metabolic/respiratory acidosis
- Hyperglycaemia

Decreased renal excretion of potassium

- Acute and chronic kidney disease: Decreased Glomerular Filtration Rate (GFR) below 30mL/min per 1.73 m^2
- Tubular dysfunction: Urinary tract infections (UTI), sickle cell disease and type 4 renal tubular acidosis (hypoaldosteronism)

Decreased effective arterial blood volume

- Functional Renal Tubular acidosis (RTA)
- Severe dehydration in infants and young children

Decreased activity of the renin-angiotensin-aldosterone system

- Congenital adrenal hyperplasia (CAH)
- Primary adrenal insufficiency – Addison's disease or crisis
- Pseudohypoaldosteronism
- Medications: potassium-sparing diuretics e.g. spironolactone, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB).

Pseudohyperkalaemia

- This is not a **true** hyperkalaemia - it is most commonly caused by haemolysed blood samples due to difficulties in obtaining or handling blood samples. Always question the results if obtaining blood has been difficult.

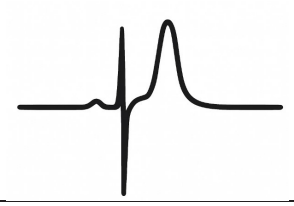
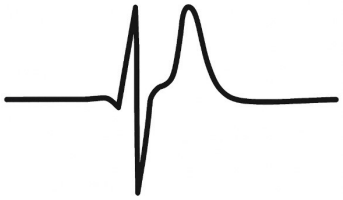
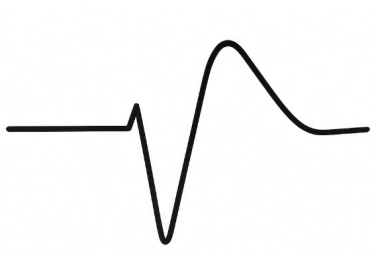
Prevention/promotion

- Promote healthy normal diet
- Avoid over-the-counter medication
- Early heathy seeking behaviour
- Appropriate and accurate fluid and electrolyte management in cases with dehydration
- Avoid haemolysis when acquiring blood sample for potassium assessment

Signs and symptoms

- A thorough clinical assessment and evaluation with history and clinical examination should be conducted to ascertain the cause
- Asymptomatic:
  - Mild elevation with serum potassium <6mmol/L
  - Moderate elevation with serum potassium between 6-7mmol/L
- Symptomatic
  - Severe elevation with serum potassium > 7mmol/L
  - Ascending muscle weakness/flaccid paralysis, decreased deep tendon reflexes
  - Constipation, abdominal distension
  - Palpitations, bradycardia, syncope, or asystole depending on the severity of cardiac conduction disturbances
- ECG changes:
  - Potassium level between 5.5 to 6.5 – Tall peaked T waves (more than 2/3 of the R wave) with a narrow base and shortening of the QT interval
  - Potassium level between 6.5 to 8.0 – Peaked T waves, prolonged PR interval, decreased or disappearing P wave, widening QRS complex, and amplified R wave
  - Potassium level above 8.0 – Absent P wave, bundle branch block, progressive widening of the QRS complex that eventually merges with the T wave to form a sinusoidal pattern. This is followed by ventricular fibrillation or asystole.

ECG Tracing with Hyperkalaemia

Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5-6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5-8.0 mEq/L)		Loss of P wave Prolonged QRS complex ST-segment elevation Ectopic beats and escape rhythms
Severe (>8.0 mEq/L)		Progressive widening of QRS complex Sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

Source: EpoMedicine

Investigations

- History – pointing towards AKI (Oliguria/Anuria)
- Laboratory investigations depending on presentation and availability should be conducted and may include:
  - Full blood count, Peripheral Blood Film (PBF), urinalysis
  - Serum electrolytes - to exclude pseudohyperkalaemia repeat the blood sample using a free-flowing or arterial blood sampling
  - Arterial blood gas analysis
  - BUN and creatinine
  - Serum lactate dehydrogenase – see haemolysis
  - Serum creatinine kinase – rhabdomyolysis
  - ECG
  - Abdominal USS and KUB

Differential diagnosis

Ascending muscle weakness/paralysis:

- Polio and West Nile virus infection, toxins (e.g. botulism), hypocalcaemia and

hypermagnesaemia and Guillain-Barré Syndrome (GBS)

Palpitation and syncope

- Life-threatening cardiac conduction abnormalities (See section on syncope)

Management

Primary level

- Stabilise the patient and refer

Secondary level

- Stop all potassium containing fluids, feeds and/or drugs
- Start managing hyperkalaemia depending on availability of resources
  - Stabilise the cardiac membrane with calcium gluconate
  - Give salbutamol nebulisation
- Discuss and refer the patient for tertiary level care

Tertiary level

- Confirm the patient truly has hyperkalaemia by obtaining venous or arterial blood sample that is not haemolysed for rapid analysis
- Admit patient to HDU or ICU

1.a . Stop all potassium containing fluids, feeds and/or drugs

1.b . Stabilize the cardiac membrane with

- 10% calcium gluconate – 60mg/kg given as a 0.5mL/kg diluted in an equal volume of normal saline. Maximum 2g (20mL, 4.5mmol) per dose IV or IO over 5 minutes
- May repeat in 10 minutes if arrhythmias or ECG changes persist
- **Do not** mix with sodium bicarbonate

1.c **.** Decrease **extracellular potassium levels with**

- Salbutamol nebulisation
  - Neonates - 0.4mg in 2mL saline
  - 5 years - 2.5mg in 2mL saline
  - >5 years – 5mg in 2mL saline
- Give 2 back-back nebs and repeat after 20 minutes If no response after 30 minutes:
- Give insulin 0.1IU/kg bolus subcutaneously with glucose 0.5g/kg (2.5mL/kg 20% glucose or 5mL/kg of 10% glucose) bolus
- Monitor glucose after 30minutes, then 1 hourly

- If no response after 30 minutes, repeat insulin and glucose dose

- If still no response after another 30 minutes:
  - Start insulin infusion 0.05 – 0.2IU/kg/hour. Give with 2-4mL/hour 10% dextrose.
  - Monitor glucose after 30 minutes then 1 hourly
  - Salbutamol IV 4µg/kg in 5mls water for injection over 20 minutes (repeat as necessary)
  - Consider 10mL/kg bolus normal saline plus 1mg/kg frusemide if patient euvolaemic or hypovolaemic

1.d **Treat metabolic acidosis**

- Sodium bicarbonate 1-2mmol/kg IV over 30 minutes

1.e **Reduce potassium body stores by**

- Peritoneal dialysis Treating the underlying cause

- Start initial management whilst consulting ICU, nephrologists, urologist as needed.
- Refractory hyperkalaemia may need to be managed with dialysis.

Hypokalaemia

Definition

Serum or plasma potassium less than 3 mmol/L

- Moderate hypokalaemia with serum potassium levels between 2.5 to 3mmol/L
- Severe hypokalaemia with serum potassium levels below 2.5mmol/L

Risk factors/causes

Gastrointestinal losses

- Profuse vomiting or diarrhoea
- Infective gastroenteritis including cholera
- Pyloric stenosis
- Pancreatitis
- Malabsorption e.g. HIV enteropathy

Urinary losses

Osmotic diuresis in DKA
Glomerulonephritis
Pyelonephritis
Tubulopathy etc.

Drugs

Diuretic therapy e.g. furosemide use, aminoglycosides and/or steroids

Decreased intake

- Malnutrition
- Prolonged IV fluids especially post-operation surgical patients on nil per os (NPO)

Intracellular shift

- Metabolic alkalosis
- Acute stress
- Insulin therapy
- High dose salbutamol

Prevention/Promotion

- Health education on balanced diet which includes food rich in potassium
- Early health-seeking behaviour
- Timely and appropriate fluid and electrolyte management
- Avoid prolonged fluid administration in post-operated cases, encourage early

feeding as soon as tolerated

Signs and symptoms

- Lethargy or coma
- Muscle weakness: Generalized muscle weakness, respiratory muscle weakness and GIT hypo- motility leading to paralytic ileus or constipation
- Hyperglycaemia
- Hypotension
- Cardiac arrhythmias
- ECG changes: Flat T-waves and ST depression
- Cardiac arrest

Diagnosis

- Clinical assessment and evaluation should include thorough history and physical examination
- Laboratory investigations should depend on presentation and availability as follows:
  - FBC, MRDT/Malaria Parasites (MPs), electrolytes, RBS, arterial blood gas analysis
  - Blood urea nitrogen (BUN) and creatinine
  - ECG
  - Abdominal X-ray, abdominal USS
  - Urine dipstick, urinalysis -microscopy, culture, and sensitivity (MCS)

Management

Primary level

- Stabilise the patient (ABCDE) and refer to next level of care

Secondary Level

- Stabilise the patient (ABCDE) and manage losses if present
- Conduct initial laboratory investigations to find the underlying cause depending on availability
- If potassium > 2.5 mmol/L and able to feed and not having on-going losses
  - Oral potassium supplement slow K 1 - 4mmol/kg/day
  - Potassium rich diet with bananas, cooked Irish potatoes, nuts, oranges etc.
- If severe hypokalaemia (<2.5mmol/L) / persistent hypokalaemia despite treatment, discuss the patient and refer to tertiary level

Tertiary Level

- Start initial management whilst consulting ICU, nephrologists, urologist
- Admit patient to HDU or ICU as indicated
- Stabilise the patient and manage losses if present
- Conduct initial laboratory investigations to find the underlying cause
- If potassium > 2.5 mmol/L and patient able to feed and not having on-going losses
  - Oral potassium supplement slow K 1 - 4 mmol/kg/day
  - Potassium rich diet with bananas, cooked Irish potatoes, nuts, oranges etc.
- If potassium < 2.5 mmol/L and/or patient is symptomatic
  - IV potassium chloride 2mmol/kg **plus** the deficit (3.5 – measured serum potassium in mmol/L)/kg.

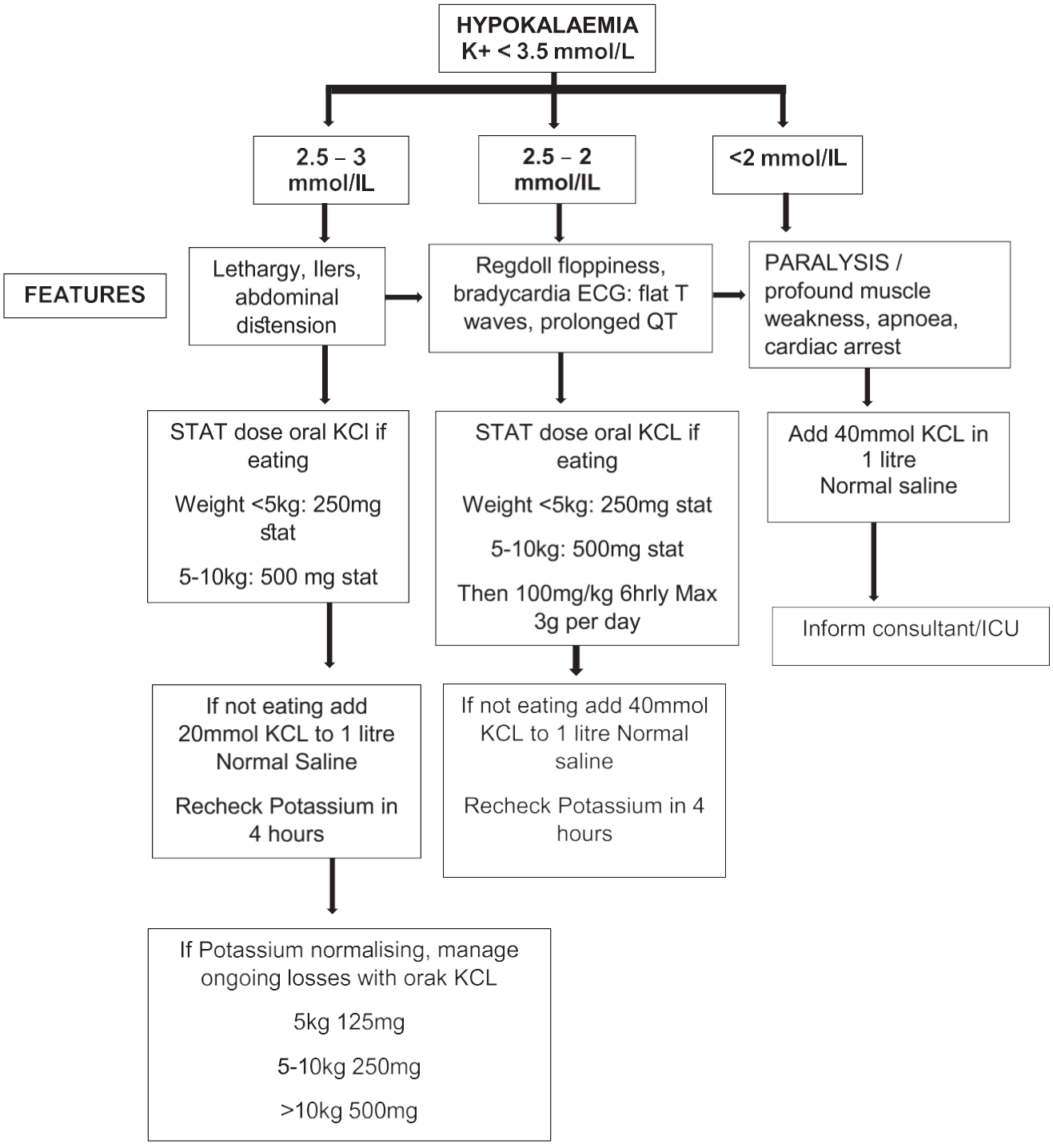
  Do not exceed 0.2mmol/L/kg /h.

Example:
7kg infant with serum potassium of 1.5mmol/L, IV potassium will be:
(2mmol x 7kg**) + [**(3.5 – 1.5mmol) x 7kg**]** = 28 mmoL in 24hrs

Do not give it as a pure infusion! Add the calculated potassium to the calculated daily maintenance fluid for the child e.g. in 700mls of fluid for the 7kg child and give at normal maintenance rate.

- **Emergency: Arrhythmias – call paediatric consultants for help**
  - Discuss the patient with seniors
  - Start 0.5 mmol/kg potassium chloride in 20mls normal saline over 30 min (Concentration should not exceed 80mmol/L)
- Monitor potassium regularly because supplemental potassium can cause hyperkalaemia
- Treat the underlying cause

Flow chart for management of hypokalaemia



Hypernatraemia

Definition

It is clinical disorder characterized by serum or plasma sodium greater than 150mmol/L.

Risk factors/causes

Inadequate water intake

- Premature infants
- Inadequate breast feeding
- Poor fluid intake during illness
- Drought

Gastrointestinal losses

- Excessive vomiting
- Profuse diarrhoea
- Loss from stomas

Urinary losses

- Central Diabetes Insipidus: inadequate production or release of ADH

  Congenital Central DI

  - Congenital central nervous system malformation
  - Genetic syndromes associated with CNS abnormalities
  - Congenital hydrocephalus

  Acquired Central DI

  - Brain tumours
  - Acquired hydrocephalus
  - Infiltrative processes of the hypothalamic-pituitary stalk
  - Neurological sequelae from neurosurgery and trauma

- Nephrogenic Diabetes Insipidus: inadequate response to circulating ADH

  Hereditary Nephrogenic DI

  - Bardet-Biedl and Bartter syndromes
  - Nephronophthisis
  - Cystinosis, and
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

  Acquired Nephrogenic DI

  - Drug toxicity is the most common cause of acquired DI: Amphotericin, demeclocycline, ifosfamide, foscarnet, and cidofovir, lithium toxicity etc.

- Chronic diseases: Obstructive uropathy, sickle cell disease, acute or chronic kidney disease
- Hypercalcemia and Hypokalaemia

Other causes of osmotic diuresis

- Renal excretion of nonelectrolyte, non-reabsorbed solutes, such as mannitol or glucose
- DKA and Hyperglycaemia

Excess skin losses

- Burns
- Excessive sweating
- Excessive heat
- Significant febrile illness
- Vigorous exercise
- Severe premature infants

Excessive salt intake/Iatrogenic causes

- Diet
- IV fluids -normal saline
- Sodium bicarbonate infusion during correction of metabolic acidosis
- Use of hypertonic saline
- Inappropriate preparation of home-made ORS

Salt poisoning

- Intentional increased salt intake in a child's diet as a form of child abuse

Signs and symptoms

Acute Hypernatraemia

- Irritability
- Restlessness
- Weakness
- muscular twitching
- In young infants high pitched-cry
- Fever and tachypnoea
- Doughy skin
- Severe symptoms with serum sodium > 160mEq/L.
- Altered mental status, lethargy, coma, and seizures

Chronic Hypernatraemia

- Hypernatraemia present more than 1 day
- There are no symptoms due to cerebral adaptation which occurs within 1 to 3 days of presentation
- Most patients with chronic hypernatraemia have underlying neurologic conditions e.g. mid-brain abnormalities

In severe cases, e.g. salt poisoning, hypernatraemia causes demyelinating and irreversible neurological brain injury.

If clinical manifestation includes insensible losses, there will be clinical signs of severe dehydration "see Dehydration".

Investigations/Diagnosis

- Elevated serum or plasma sodium level above 150 mEq/L
- Serum or plasma electrolytes
- Serum or plasma BUN and creatinine
- Urine electrolytes
  - Low urine sodium <25 mEq/L - hypernatraemic hypovolaemia due to GIT losses
  - High urine sodium exceeding 200 mEq/L - suspect salt poisoning
- Fraction excretion of Sodium (FENa)

$$FENa = \frac{\text{Serum Cr (µmol/l) x Urinary Na (mmol/L)*}}{\text{Serum Na (mmol/L)}} X$$

*From morning void collection

FENa = > 2% - Suspect salt poisoning
FENa = < 1% - Suspect hypenatraemia caused by water loss

- Urine osmolality

Urine osmolality > plasma osmolality	Normal ADH response - suspect water losses from the GIT or skin
Urine osmolality < plasma osmolality	Abnormal ADH response causing urine concentration defect manifested by polydipsia, polyuria and less concentrated urine

Management

Primary level

- Assess the hydration status
- Refer
  - All cases with history of vomiting and diarrhoea not tolerating Plan A with oral rehydration solution (ORS) to secondary hospital facilities (see management of dehydration - Plan A)
  - All cases with signs of severe dehydration
  - All cases with history of losses and clinical signs suggestive of hypernatraemia
- Refer the cases after inserting an IV line and commenced on intravenous maintenance fluid (see calculation of maintenance fluids in management of dehydration).
  - The prescribed fluids should be Ringer's lactate or 0.9 percent (normal) saline
  - If IV access is not possible, insert NGT for ORS and give ORS according to Plan A or B depending on level of dehydration (see management of dehydration)

Secondary level

- Assess hydration status
- Start initial management of severe dehydration as per protocol (see management of dehydration)
- Initial investigations
  - MPs/MRDT
  - FBC
  - BUN and creatinine
  - Serum or plasma electrolytes
  - Blood culture and Lumbar puncture if suspected sepsis or meningitis
- Start treating the underlying cause and cover for sepsis or meningitis if suspected
- Catheterize and monitor input and output
- Once a diagnosis of hypernatraemia is made, discuss and refer the patient to a tertiary level facility

Tertiary level

- Initial management as in secondary above

Note : Fluid resuscitation with isotonic fluid to restore intravascular volume and tissue perfusion takes precedence over correction of the hypernatremia

Correction of Hypernatraemia

- When managing hypernatraemia in paediatrics, these questions must be addressed:
  1. What is the volume status of the patient?
  2. Is there an emergent need for fluid resuscitation to restore intravascular volume and tissue perfusion?
  3. What is the magnitude of the water deficit that needs to be restored?
  4. At what rate should the hypernatremia be corrected (as lowering the sodium concentration too rapidly may lead to neurologic injury)?
  5. Is there a concurrent ongoing fluid loss that needs to be addressed?
  6. What is the underlying cause of hypernatremia and are there specific interventions that need to be considered?
- Calculating the free water deficit and rate of administration:
  - The volume of free water to be provided can be calculated using one of two common approaches:

METHOD 1:
Free water deficit (mL) =
Current total body water x ([current plasma Na/140] - 1)
Estimating total body water (TBW) as 60% of the child's body weight (kg) (0.6 L/kg)

Thus, in a 6 kg infant with a plasma sodium of 160, the free water deficit

METHOD 2:
Free water deficit (mL) =

(4 mL/kg) x (weight in kg) x (desired change in plasma Na)

Thus, for this the 6 kg infant described above with plasma sodium elevated 20 mEq/L above desired (160 – 140), his or her water deficit would be:

Note: The variation in free water needed between the two calculations is generally clinically negligible. The calculated volumes are estimates and correction requires laboratory results and clinical exams to guide on-going changes.

In children with chronic hypernatremia (plasma sodium ≥150 mEq/L for greater than 24 hours) or those with acute severe hypernatremia (plasma sodium >160 mEq/L), it is recommended that a rate of correction does not exceed a fall of sodium greater than 0.5 mEq/L per hour (i.e., 10 to 12 mEq/L/day).

Prescribed fluids:

- The total fluids given should be the daily maintenance **plus** the free water deficit.
- The deficit should be corrected over 24 - 48hrs to avoid complications.
- Most administered fluid contains sodium, but IT is hypotonic to the patient's plasma, thereby providing free water.
- Can use 0.45 percent saline which is hypotonic to the patient's plasma
- Normal saline (0.9 percent saline) is isotonic in patients with normal plasma sodium, BUT, it is a hypotonic fluid for children with hypernatremia, therefore it can be used as initial rehydration fluid for patients with Hypernatraemic hypovolaemia.
- Enteral fluids including oral rehydration solution (ORS) are also typically hypotonic fluids.

- **Ongoing losses and maintenance needs**
  - The above calculations correct free water losses that have occurred up to the time of presentation.
  - Children have ongoing normal maintenance needs and may also have

excess free water losses not accounted for by calculations for maintenance fluids (e.g. continuing diarrhoea or persistent fever), therefore, should receive replacement of these ongoing losses to prevent further electrolyte derangement.
  - Calculate the water deficit
  - Calculate maintenance fluids accounting for insensible losses

- **Monitoring**
  - Monitor clinical progress regularly every 30 minutes for the first 2 hours then 4 hourly regularly for improvement or deterioration (check mental status, seizures or coma, dehydration status, neurological status, fluid intake and urine output)
  - Monitor serum/plasma electrolytes every 6 hours if a blood gas analyser is available; BUN and creatinine every 24 hours. If not available monitor every 24 hours

Consult paediatric nephrologist in all cases with no improvement or with clinical deterioration including development of AKI after 24 hours

Clinical example:

A 10 kg child (TBW 0.6 x body weight) is estimated to have a 10 percent hypovolemic loss (approximately 1 L of fluid) and a serum/plasma sodium concentration of 156 mEq/L. The following calculations can be made:

Total fluid deficit: 10 percent of 10 kg = 1 L (1000 mL)
Free water deficit: 6 L [(156/140 mEq/L) - 1] = 0.686 L (686 mL)
Isotonic loss: Total fluid deficit - Water deficit = 1000 mL – 686 mL = 314 Ml

During resuscitation:
Received 20ml/kg bolus = 20ml x 10 kg = 200mls
Remaining isotonic fluid loss = 314 mL – 200 mL = 114 mL

Replace the remaining fluid deficit over 36 hours so that the sodium is lowered at a rate below 0.5mEq/L per hour:
Free water deficit replacement is 686 mL in 24 hours = (686 mL/3) x 2 = about 460 mL
Maintenance fluid is 100 mL x 10kg = 1000 mL/day
Remaining isotonic fluid loss = 314 mL – 200 mL = 114 mL (excess on going losses of fluid and electrolyte)

Therefore, the rate of fluid replacement using 0.45 percent saline = 65 mL / hour

Follow up

- Follow up all uncomplicated cases in general clinic in a month
- Follow up all complicated cases in renal clinic if they had AKI
- Follow all complicated cases with neurological sequelae in neurology clinic

Hyponatremia

Definition

Hyponatraemia is defined as serum or plasma sodium level < 135 mEq/L.

- Mild hyponatraemia – serum concentration between 130 and 134 mEq/L
- Moderate hyponatraemia – serum concentration between 120 to 129 mEq/L
- Severe hyponatraemia – serum concentration <120 mEq/L
- Hyponatraemia is further classified as:
    - Acute hyponatraemia developing over a period of less than 48 hours – risk of cerebral oedema
    - Chronic hyponatraemia is defined as hyponatraemia that has been present for more than 48 hours

Causes/risk Factors

Hypotonic hyponatraemia

Hyponatraemia due to loss of sodium as well as free water, or due to excess free water retention

Hypovolaemia and persistent antidiuretic hormone (ADH) levels:

- Hyponatraemia due to loss of sodium in excess of water
- Urinary salt wasting in obstructive uropathy
- Skin losses in cystic fibrosis

Normovolaemia and inappropriate ADH levels:

- Excess water intake (suppresses ADH release, allowing free water excretion and the generation of a dilute urine)
- Pulmonary and oncologic disorders
- Recent surgery
- Central nervous system (CNS) injury or infection
- Endocrine disorders
- Medications e.g. some anticonvulsants and chemotherapeutic drugs

Normovolaemia

- Primary polydipsia
- Reset osmostat (a condition with a lower-than-normal plasma osmolality threshold for ADH release)

Hypervolaemia

- Excess water retention, promoted by a decrease in kidney perfusion and urine output leading to a drop in serum sodium leading to decreased effective circulating volume (ECV).

    - Nephrotic syndrome
    - Liver cirrhosis
    - Heart failure
  - Kidney failure with a decrease in GFR, resulting in water retention, leading to a drop in serum sodium.

- **Hyponatraemia without Hypotonicity**

  Increased tonicity
  - Endogenous sources e.g. hyperglycaemia and increased urea (azotaemia)
  - Exogenous sources e.g. mannitol and sorbitol

- **Pseudohyponatraemia**
  - Common in patients with hyperlipidaemia or hyperproteinaemia.
    - Total parenteral nutrition (TPN)
    - Hyperproteinaemia is uncommon in children
  - Always confirm the laboratory method used to measure sodium before interpreting the results in patients with confirmed hyperlipidaemia or hyperproteinaemia

Promotion/Prevention

- Avoid administration of unrestricted hypotonic fluids to at risk paediatric population intravenously or by mouth. They are at risk of developing syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
- At-risk population include postoperative cases, children with central nervous system injury or illness (e.g. meningitis or encephalitis etc.) and those with respiratory disorders (e.g. pneumonia or bronchiolitis).
- Prescribe fluids accurately and correct any electrolyte imbalance to avoid giving excessive free water

Signs and symptoms

- History and physical examination with focus on the following:
  - Fluid loss e.g. vomiting and diarrhoea, excessive water intake, excessive salt loss, medications, administration of TPN
  - Medical conditions associated with unsuppressed ADH release e.g. CNS injury or infections, pulmonary diseases, immobilisation etc.
  - Anuria or oliguria, oedema and ascites with reduced Effective Circulating Volume (ECV (e.g. nephrotic syndrome, liver failure and heart failure)
- Acute hyponatraemia:
  - Patients are more likely to be symptomatic and symptoms dependent on the severity of hyponatraemia
  - Sodium >125 mEq/L: minimal specific symptoms related to hyponatraemia

    - Sodium below 125 mEq/L: some neurologic symptoms observed e.g. nausea and malaise
    - Sodium below 120 mEq/L: may present with headache, lethargy, obtundation, and seizures.
    - In severe cases, brain herniation and death may occur.
- Chronic hyponatraemia:
    - Usually asymptomatic
    - May present with subtle neurologic manifestations such as restlessness, weakness, fatigue, or irritability
    - If some acute event causes rapid decreases in sodium level in chronic hyponatraemia the patients may present as in severe acute hyponatraemia (Acute-on-chronic presentation)

Investigations

Laboratory investigations should include:

- RBS, serum BUN, creatinine and electrolytes
    - Hyponatraemia and hyperkalaemia may be a sign of adrenal insufficiency
- Urine dipstick
- Other tests:
    - Lipemic plasma and serum tests to exclude pseudohyponatremia
    - Serum osmolality and tonicity – hyponatraemic children are hypotonic with serum osmolality lower than the normal <275 mOsm/kg
    - Urine osmolality
        - **Hyponatraemia and hypotonicity**, urine osmolality >100 mOsm/kg is indicative of impaired water excretion - SIADH and renal impairment
        - **Hyponatraemia and increased total body water (oedema)**, urine osmolality >100 100 mOsm/kg is indicative of reduced ECV, leading to ADH release - nephrotic syndrome, heart failure, and liver cirrhosis
        - **Hyponatraemia and dilute urine**, urine osmolality <100 mOsm/kg, the differential diagnosis includes:
            - Psychogenic polydipsia
            - Reset osmostat
            - Salt-losing nephropathy

Plasma and Urine osmolality and Plasma tonicity measurement

Plasma osmolality (Posm)
It is the **ratio** of plasma solutes and plasma water. The normal Posm is 275 to 290 mosmol/kg. Estimated Posmo calculation:

If glucose and urea reported in mg/Dl:
Posm = 2 x [Na] + [Glucose]/18 + Blood urea nitrogen/2.8

If Glucose and urea reports in mmol/L:
Posm = 2 x [Na] + [Glucose] + [Urea]

Urine osmolality (Uosm)
Uosm can be calculated from the urine concentrations of sodium (Na), potassium (K), and urea when there is no marked glucosuria and metabolic acidosis:

If urea reported in mg/dL:
Uosm = 2 (Urine Na + Urine K) + Urine [Urea ÷ 2.8]

If urea is reported in mmol/L the formula is:
Uosm = 2 (Urine Na + Urine K) + Urine [Urea]

Plasma Tonicity
It is the **effective** plasma osmolality.

If glucose is measured in mg/dL:
Plasma tonicity = 2 x [Na] + [Glucose]/18

If glucose is measured in mmol/L:
Plasma tonicity = 2 x [Na] + [Glucose]

Management

- Relieve the symptoms of hyponatraemia
- Avoid too rapid correction to prevent central nervous system (CNS) complications
- Prevent a further decline in sodium concentration
- Determining and treating the underlying cause
- Treatment approach depends on:
  - Duration of hyponatraemia – Acute versus chronic hyponatraemia
  - Severity of hyponatraemia based on the presence and severity of symptoms
- Frequent monitoring to reassess and adjust therapy based on clinical examinations and follow-up laboratory evaluation, including subsequent assessment of sodium levels.

Primary level

- Assess the hydration status
- Refer to secondary hospital facilities:
  - All cases with a history of vomiting and diarrhoea not tolerating Plan A with ORS (see management of dehydration - Plan A)
  - All cases with signs of severe dehydration
  - All cases with clinical signs suggestive of hyponatraemia
- Refer the patient after inserting an IV line and after commencing intravenous maintenance fluid: Normal saline (0.9%)
- If IV access not possible, insert NGT and commence Plan B with ORS and refer as soon as
- possible.
- Replace on going losses with ORS as in Plan A using NGT if the child is not able to drink

Secondary level

- Assess hydration status
- Start initial management of severe dehydration (see management of dehydration)
- Initial investigations: MPS, FBC, BUN and creatinine, serum or plasma electrolytes
  - Blood culture and Lumbar puncture if one suspects sepsis or meningitis
- Start treating the underlying cause and cover for sepsis or meningitis if suspected
- Catheterise and monitor input and output

Sodium Correction

Asymptomatic hyponatraemia:
Treat the underlying cause
If hyponatraemia is not being corrected, then concurrently give normal saline and correct any associated electrolyte imbalance

Mild to Moderate symptomatic hyponatraemia:
If no hypovolemia: Fluid restriction
If hypovolemia present: correct hydration with normal saline IV
Aim to not exceed increase in serum sodium concentration by 0.5 mmol/L/hour

- Monitor clinical progress regularly every 30 minutes for the first 2 hours then every 4h ours regularly for improvement or deterioration (check mental status, seizures or coma, dehydration status, neurological status, fluid intake and urine output)
- Monitor serum/plasma electrolytes, BUN and creatinine regularly at least every 24 hours if a blood gas analyser is not available

- Refer all cases with no improvement or with clinical deterioration including development of AKI after 24 hours
- Refer all cases with severe hyponatraemia

Tertiary level

- Manage mild and moderate hypernatremia as in secondary level above.

Acute hyponatraemia

- There is inadequate cerebral adaptation. Saline therapy should be given to all symptomatic patients to prevent development of complications of hyponatraemia

Severe hyponatraemia (seizures, obtundation, and coma):

- Give hypertonic saline (3% saline) at rate of 1-2ml/kg/hour. Aim to raise sodium by 8-9mmol/L over the initial 24 hours.
- If hypertonic saline is not available, give homemade NaCl via NGT
  - 1 teaspoon of salt = 17mmol
  - Mix 1 teaspoon of salt in 15mL of water and give 5mL= 5.7mmol
  - This dose should be given once daily.
  - Aim to increase serum sodium by 3mmol/L.
- Check serum Sodium 6 hourly after the administration of oral dose. If there is no increase in sodium or further reduction in sodium, repeat the oral dose.

Sodium correction in chronic hyponatraemia

- Cerebral adaptation has occurred therefore if plasma sodium is corrected too quickly, the patient is at risk of osmotic demyelination
- Identify and treat the underlying cause
- **In cases where the patient has chronic hyponatraemia with acute exacerbation leading to symptomatic presentation then initiate therapy as for acute hyponatremia to increase serum sodium levels.**

Sodium correction in unknown classification

- Duration of hyponatraemia is unknown.
- Treat patients as in chronic hyponatraemia
- If symptomatic, then correct hyponatraemia by giving normal saline (0.9%) to increase the concentration of sodium

- Monitor clinical progress regularly every 30 minutes for the first 2 hours then 4hourly regularly for improvement or deterioration (check mental status,

seizures or coma, dehydration status, neurological status, fluid intake and urine output)
- Monitor serum/plasma electrolytes every 6 hours if available, BUN and creatinine every 24 hours.
- Consult a paediatric nephrologist/endocrinologist (as appropriate) if there is no improvement or with clinical deterioration including development of AKI after 24 hrs

Follow up

- Follow up all uncomplicated cases in the general clinic in a month
- Follow up all complicated cases with AKI in the renal clinic
- Follow all complicated cases with neurological sequelae in the neurology clinic

Calcium

The normal ranges of ionized serum or whole blood varies with age.

Neonates 1 month	5.2 to 6.1 mg/dL (1.29 to 1.52 mmol/L)
Infants 3 months	5.2 to 6.0 mg/dL (1.30 to 1.49 mmol/L)
Infants 12 months	5.0 to 5.6 mg/dL (1.24 to 1.39 mmol/L)

After 12 months of age:
Ionized calcium – 4.65 to 5.25 mg/dL (1.2 - 1.3 mmol/L)
Total calcium – 8.5 to 10.5 mg/dL (2.12 - 2.62 mmol/L)

Normal ranges of calcium according to age

Distribution of total serum calcium

- 15 percent of serum calcium is bound to multiple organic and inorganic anions such as sulphate, phosphate, lactate, and citrate
- 40 to 45 percent of serum calcium is bound to proteins, primarily albumin
- The remaining 40 to 45 percent serum calcium circulates as physiologically active ionized (or free) calcium

Hypercalcaemia

Definition

A clinical condition in which serum or plasma calcium concentration >11 mg/dL (2.75 mmol/L)

- **Mild hypercalcemia** – Serum or plasma calcium above the upper limit of normal but <12 mg/dL [3 mmol/L])
- **Moderate hypercalcemia** –serum or plasma calcium concentration between 12 to 14 mg/dL (3 to 3.5 mmol/L)
- **Severe hypercalcemia** – serum or plasma calcium concentration >14 mg/dL [3.5 mmol/L])
- Serum or plasma calcium concentrations >15 mg/dL (3.75 mmol/L) are life threatening

Risk Factors / Causes Parathyroid-mediated

- Primary hyperparathyroidism
- Secondary hyperparathyroidism e.g. severe CKD
- Familial hypocalciuric hypercalcaemia (autosomal dominant disorder)
- Metaphyseal chondrodysplasia: A rare form of dwarfism – Jansen-type metaphyseal chondrodysplasia

Non-parathyroid mediated

- Malignancy e.g. most solid tumours and leukaemia
- Hypervitaminosis D
- Immobilisation: occurs due to a non-parathyroid-mediated increase in bone resorption
- Medications e.g. Lithium, thiazide diuretics, PTH or PTHrP analogues
- Increased calcium intake
    - Chronic kidney disease treatment
    - Milk-alkali syndrome: Excess calcium carbonate supplementation to treat osteoporosis or dyspepsia
- Hypervitaminosis A: Retinoic acid causes a dose-dependent increase in bone resorption
- Theophylline toxicity

Endocrine disorders

- Thyrotoxicosis - thyroid hormone-mediated increase in bone resorption
- Pheochromocytoma - Tumour production of Parathyroid Hormone -related Protein (PTHrP)

- Adrenal insufficiency – there is increased bone resorption, increased proximal tubular calcium reabsorption and increased binding of calcium to serum proteins

Miscellaneous causes

- Rhabdomyolysis associated with acute renal failure - mobilisation of calcium deposited in the injured muscle
- Congenital lactase deficiency - increase in calcium absorption in the ileum in the presence of non-hydrolysed lactose.

Prevention/ Promotion

- Early detection and treatment
- Appropriate dosing of calcium, vitamin D and vitamin A

Signs and symptoms

- Asymptomatic
- GIT symptoms e.g. anorexia, nausea, vomiting, and constipation, pancreatitis and Peptic Ulcer Disease (PUD)
- Cardiovascular e.g. hypertension, bradycardia, short QT interval
- Renal e.g. polydipsia, polyuria, nephrocalcinosis, renal insufficiency, renal tubular acidosis
- Dermatological e.g., pruritus
- Neurologic e.g. headache, irritability, weakness, and lethargy, seizures, confusion, stupor, coma and death
- Neuropsychiatric e.g. behavioural changes, delirium, anxiety, depression

Investigations

- Exclude malaria with MPS and MRDT
- Blood culture
- Lumbar puncture for CSF analysis
- BUN and creatinine
- Serum electrolytes including calcium, magnesium and phosphate (CMP)
- Parathyroid hormone
- Vitamin D
- Serum albumin, total protein and liver function tests
- Urine dipstick, Urine MCS
- Plain abdominal X-ray
- Cardiac echocardiography and electrocardiography (ECG)
- Abdominal USS and KUB

- Abdominal CT scan or MRI
- Brain CT scan or MRI

Differential diagnosis

- Acute gastroenteritis
- Sepsis, meningitis, encephalitis
- Hyperparathyroidism
- Chronic kidney disease
- Hypervitaminosis D and A
- Pancreatitis
- Addison crisis
- Malignancies
- Neonatal subcutaneous fat necrosis

Management

- Treat the presenting symptoms
- Treat the underlying cause
- Mild and moderate hyper calcium do not need immediate treatment but should avoid aggravating factors e.g.
  - Thiazide diuretics,
  - Lithium,
  - Volume depletion,
  - Prolonged bedrest/inactivity,
  - High calcium diet >1000mg/day,
  - Calcium supplements,
  - Vitamin D supplements> 800u/day
  - Ensure adequate hydration

Primary level

- Thorough clinical assessment
- Treat emergency presenting symptoms
- Refer all complicated cases to secondary level

Secondary level

- Thorough clinical assessment
- Initial lab work-up to exclude malaria, sepsis or meningitis, BUN and creatinine, serum electrolytes and calcium magnesium phosphate (CMP), liver function test, total protein and albumin level
- Urine work-up
- Initial imaging:

- CXR, plain abdominal X-ray, abdominal USS and KUB
- Start treatment for possible sepsis or meningitis if suspected
- Start treating for hypercalcaemia with furosemide
  - Start furosemide 1-2mg/kg/dose (maximum 6mg/kg/day in divided doses twice or three times a day) to increase calcium excretion.
- Reassess and monitor regularly the clinical and laboratory improvement of hypercalcaemia

Refer to tertiary level if there are no signs of improvement.

Tertiary level

- Thorough clinical assessment
- Initial lab work-up to exclude malaria, sepsis or meningitis, BUN and creatinine, serum electrolytes and CMP, liver function test, total protein and albumin level
- Urine work-up
- Initial imaging:
  - CXR, plain abdominal X-ray, abdominal USS and KUB, cardiac echo, ECG
- Start treatment for possible sepsis or meningitis if suspected.
- Start treating for hypercalcaemia with furosemide
  - Start furosemide 1-2mg/kg/dose (maximum 6mg/kg/day in divided doses twice or three times a day) to increase calcium excretion.
  - Reassess and monitor regularly the clinical and laboratory improvement of hypercalcaemia

Note: Consult paediatric nephrologist or endocrinologist as needed for severe hypercalcaemia.

Hypocalcaemia

Definition

Hypocalcaemia is a clinical condition characterised by a physiological reduction of calcium concentration in the body.

- Serum ionised free calcium < 4.4mg/dL (1.1 mmol/L)
- Total serum calcium < 8mg/dL (2 mmol/L)

Causes/Risk factors

1. Decreased Calcium intake or Vitamin D intake
2. Neonatal Hypocalcaemia: Early/late transient neonatal hypocalcaemia and persistent neonatal hypocalcaemia
3. Decreased PTH

   Genetic:
   - DiGeorge syndrome
   - HDR syndrome (hypoparathyroidism, deafness, renal anomaly),
   - Mutations interfering with parathyroid gland development (X-linked)
   - Mitochondrial disorders e.g. MELAS syndrome, Kearns-Sayre syndrome)

   Autoimmune:
   - APS1, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome Other:
   - Parathyroid or thyroid gland surgery or Infiltration of parathyroid gland (e.g., iron overload, copper deposition in patients with Wilson disease etc.)
4. Decreased Vitamin D
   - Defects in vitamin D metabolism
   - Hepatic dysfunction
   - Renal dysfunction
   - Genetic disorders e.g. 25-hydroxylase deficiency, 1-alpha-hydroxylase deficiency (previously known as vitamin D-dependent rickets type 1 or pseudovitamin D-deficient rickets)
   - Defects in vitamin D action: Hereditary resistance to vitamin D (previously known as vitamin D-dependent rickets type 2)
5. Decreased Calcitonin hormone
6. Drugs
   - Bisphosphonates, denosumab, calcimimetics (cinacalcet), foscarnet, and some chemotherapeutic drugs
7. Miscellaneous:
   - Hungry bone syndrome, osteopetrosis, sepsis or acute severe illness, Gram-negative sepsis, toxic shock syndrome, HIV infection, hyperphosphatemia, alkalosis, intravenous products with citrate or lactate

(e.g. transfusion with any blood products), pancreatitis, fluoride poisoning and hypomagnesemia etc.

Prevention/Promotion

- Early detection and treatment
- Appropriate drug prescription and drug dosing
- Health education
- Advocate for a balanced diet with food rich in calcium and vitamin D
- Advocate for food fortification with calcium and vitamin D
- Advocate for breast milk fortification with vitamin D

Signs and symptoms

- Hypocalcaemia presentation is divided into acute and chronic hypocalcaemia
- Acute manifestations of hypocalcaemia
    - Tetany - increased peripheral neuromuscular irritability, electromyographically (EMG), shows repetitive, high-frequency discharges after a single stimulus
    - Trousseau's sign - induction of carpal spasm by inflation of a sphygmomanometer above systolic blood pressure for three minutes. Carpal spasm, is characterised by adduction of the thumb, flexion of the metacarpophalangeal joints, extension of the interphalangeal joints, and flexion of the wrist
    - Chvostek's sign - contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear
    - Cardiovascular – hypotension, ECG with prolongation of the QT interval and Congestive cardiac failure (CCF)
    - Papilledema – in severe hypocalcaemia
    - Seizures
- Chronic manifestations of hypocalcaemia:
    - Extrapyramidal signs, Parkinsonism, dementia and subcapsular cataracts, abnormal dentition and dry skin.
- Disease specific presentation: features of the underlying disease e.g.
    - Hypoparathyroidism (see hypothyroidism)
    - Pseudohypoparathyroidism (see pseudohypoparathyroidism)
    - Vitamin D deficiency
    - Autosomal dominant hypocalcaemia

Investigations

- Exclude hypoglycaemia: RBS
- Exclude infections: FBC, MPS, blood culture, lumbar puncture

- Liver function test: Liver enzymes (AST, ALT, GGT)
- Total protein and albumin
- Renal function test: BUN + creatinine
- Blood gas: calcium, acid-base balance
- Serum electrolytes + CMP
- Serum PTH, serum vitamin D levels
- ECG, EMG (if available)
- Imaging:
    - Cranial USS
    - Cardiac echo
    - abdominal USS + KUB
    - CT brain or MRI

Calculation of corrected calcium

Calcium is mainly bound to albumin in the blood. In cases of hypoalbuminaemia, measurement of total calcium may not reflect the true levels of ionized or free calcium in the blood. Therefore, free or ionized calcium is the recommended measurement for clinical decisions (gold standard). The calcium correction formula is used when there is hypocalcaemia in the setting of hypoalbuminaemia. The formula assumes that for every 1g/dl (10g/L) fall of albumin is equal to 0.8mg/dl fall in serum calcium.

E.g. Serum total calcium concentration = 8 mg/dL (2 mmol/L) Serum albumin concentration = 2 g/dL (20 g/L) below normal,

The corrected calcium = 8mg/dL + (2x 0.8 mg/dL) = 9.6 mg/dL (2.4 mmol/L) which is normal.

Differential diagnosis

- Sepsis or meningitis
- Renal failure or CKD
- Liver failure
- Congestive cardiac failure
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Vitamin D deficiency

Management

Primary level

- Assess the patient for signs of hypocalcaemia
- Treat the emergency presenting symptoms
- Refer all patients suspected of hypocalcaemia

Secondary level

- Assess the patient for signs of hypocalcaemia
- Treat the emergency presenting signs
- Start initial investigations
- Start treating for acute hypocalcaemia, aiming to stabilize the patient:

Mild symptomatic acute or chronic hypocalcaemia:

- Give 1 to 2 g of elemental calcium using calcium carbonate or calcium citrate daily in divided doses

- Refer to tertiary level for further management and investigations

Tertiary level

- Assess the patient for signs of hypocalcaemia
- Treat the emergency presenting signs
- Start initial investigations
- Start treating for acute hypocalcaemia, aiming to stabilize the patient

Mild symptomatic acute or chronic hypocalcaemia management:

- Give 1 to 2 g of elemental calcium using calcium carbonate or calcium citrate daily in divided doses

Severe symptomatic and/or acute hypocalcaemia management:

- Intravenous calcium dosing:
  - 1-2ml/kg intravenous 10% calcium gluconate over 10 minutes (dilute 1:1 with normal saline). Repeat dose if necessary.
- Monitor for bradycardia on a monitor.
- Give a maintenance dose of 5ml/kg/day in maintenance intravenous fluids or divided into 4-6
- doses orally with feeds.
  - If given orally dilute at least 50% by feeds or water.

Check for hypomagnesaemia:

- Hypomagnesaemia is a common cause of hypocalcaemia by inducing PTH resistance and secretion
- Correct hypomagnesaemia first before correcting hypocalcaemia.
- If magnesium levels are not possible, give one dose of the magnesium

sulphate.
    - If magnesium is low, give 2g (16 mEq) of magnesium sulphate bolus by adding to 10% dextrose solution and infuse over 10 to 20 minutes, then give 1 gram (8 mEq) in 100 mL 10% dextrose per hour.
    - Continue magnesium slow infusion as long as the serum magnesium concentration is less than 0.8 mEq/L (1 mg/dL or 0.4 mmol/L).
- Persistent hypomagnesemia as seen in patients with ongoing GIT losses (e.g., malabsorption) or renal losses requires oral magnesium supplementation of 300 to 400 mg daily, divided into three doses.

Hypocalcaemia due to hypoparathyroidism:
- Patients with hypoparathyroidism require lifelong calcium and vitamin D supplementation (see management of hypoparathyroidism)

Hypocalcaemia due to vitamin D deficiency:
- Is treated with ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3).
- Give oral vitamin D2 and D3 50,000 IU weekly for 6 to 8 weeks if available.

Hypocalcaemia due to chronic kidney disease:
- Few patients with chronic kidney disease develop symptomatic hypocalcaemia
- Treat with oral calcium to bind intestinal phosphate and to prevent bone disease

Chronic liver disease:
- Give vitamin D metabolites to treat hypocalcaemia especially when there is abnormal vitamin D metabolism (renal or liver disease)
- Haemodialysis is often indicated in patients with symptomatic hypocalcaemia

- Involve the dietician in the management of the case
    - Consult a Paediatric endocrinologist, gastroenterologist, nephrologist and infectious disease specialist if available

Follow up
- Follow up in the paediatric general clinic
- Follow up in the renal clinic if the patient has renal disease
- Follow up in gastroenterology clinic if there is a malabsorption complication

Magnesium

Normal serum or plasma magnesium concentration ranges from 1.7 to 2.1 mg/dL (0.70 to 0.85mmol/L).

Hypomagnesaemia

Definition

Serum or plasma magnesium concentration below 1.7mg/dL (0.7mmol/L)

Causes/Risk factors

Gastrointestinal losses:

- Diarrhoea, malabsorption and steatorrhoea, and small bowel bypass surgery
- Acute pancreatitis
- Medications – PPIs
- Genetic disorders - intestinal hypomagnesemia with secondary hypocalcaemia

Renal losses:

- Medications
  - Diuretics e.g. loop and thiazide
  - Antibiotics e.g. aminoglycoside, amphotericin, pentamidine etc.
  - Cancer drugs e.g. calcineurin inhibitors, cisplatin etc.
  - Antibodies targeting epidermal growth factor (EGF) receptor e.g. cetuximab, panitumumab, matuzumab etc.
- Volume expansion
- Uncontrolled diabetes mellitus
- Hypercalcaemia
- Acquired tubular dysfunction
  - Recovery from acute tubular necrosis
  - Post-obstructive diuresis
  - Post-kidney transplantation
- Genetic disorders
  - Bartter/Gitelman syndrome
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
  - Renal malformations and early-onset diabetes mellitus

Health promotion

- Health education
- Early screening and treatment

Signs and symptoms

- Neuromuscular manifestations - Neuromuscular hyperexcitability (e.g. tremors, tetany and convulsions), weakness, apathy, delirium, and coma.
- Cardiovascular manifestations - ECG changes - widening of the QRS and peaking

of T waves with moderate magnesium depletion and widening of the PR interval, diminution of T waves, and atrial and ventricular arrhythmias with severe depletion.
- Signs and symptoms of associated hypocalcaemia, hypoparathyroidism, parathyroid hormone (PTH) resistance, and decreased synthesis of calcitriol
- Signs and symptoms of hypokalaemia

Differential diagnosis

- Sepsis
- Acute gastroenteritis
- Malabsorption disorders
- Electrolyte imbalance especially hypokalaemia and hypocalcaemia
- Hypercalcaemia
- Acute pancreatitis
- Diabetes mellitus
- Acquired tubular dysfunction
- Genetic disorders associated with hypomagnesaemia
- Fluid overload and drug induced hypomagnesaemia

Investigations

- Exclude diabetes mellitus: RBS
- Exclude infection: FBC, MPS, blood culture, urine culture, lumbar puncture
- Renal function tests: BUN and creatinine
- Electrolytes + CMP + ECG
- Measure 24-hour urinary magnesium excretion or
- Measure fractional excretion of magnesium (FEMg) on a random urine specimen
    - A 24-hour urine collection with magnesium excretion of 10 to 30 mg or a FEMg above 3-4% in a person with hypomagnesaemia and normal kidney function indicates renal magnesium wasting

Calculation of FEMg

$$FEMg \quad \frac{UMg \times PCr}{(0.7 \times PMg) \times UCr} \times 100\%$$

U = Urinary, P = Plasma, Mg = Magnesium, Cr = Creatinine

Management

Primary level

Assess the patient and refer

Secondary level

- Thorough history and examination
- Exclude hypoglycaemia: RBS
- Exclude infection: FBC, blood culture, urine culture, lumbar puncture
- Renal function tests: BUN and creatinine
- Electrolytes + CMP + ECG
- Start treating symptomatic hypomagnesaemia
  - Give 1 to 2 grams of magnesium sulphate [8 to 16 mEq (4 to 8 mmol)] in 50 to 100 mL of 5% dextrose over 30 to 60 minutes.
  - Repeat bolus if still symptomatic.
- Refer to tertiary level after initial stabilisation

Tertiary level

- Thorough history and examination
- Exclude hypoglycaemia: RBS
- Exclude infection: FBC, blood culture, urine culture, lumbar puncture
- Renal function tests: BUN and creatinine
- Electrolytes + CMP + ECG
- Start treating for hypomagnesaemia
  - Give 1 to 2 grams of magnesium sulphate [8 to 16 mEq (4 to 8 mmol)] in 50 to 100 mL of 5% dextrose over 30 to 60 minutes.
  - Repeat bolus if still symptomatic.
  - If still hypomagnesaemic give a magnesium infusion of 4 to 8 g of magnesium sulphate [32 to 64 mEq (16 to 32 mmol)] slowly over 12 to 24 hours.
  - Aim to maintain serum or plasma magnesium concentration above 1 mg/dL (0.4 mmol/L or 0.8 mEq/L)
- Look for other possible associated disorders
- Involve paediatric nephrologists, gastroenterologist and endocrinologist

Follow-up

- Review in general clinic after 2 weeks
- Review in renal clinic if presence of renal disease
- Review in endocrinology clinic if the patient has an associated endocrine disorder (if available)

Hypermagnesaemia

Definition

Hypermagnesaemia is a serum or plasma concentration above 2.1 mg/dL (0.85mmol/L).

Causes/risk factors

- Neonatal hypermagnesaemia that results from maternal administration of magnesium sulphate due to eclampsia.
- Iatrogenic hypermagnesaemia caused after administration of magnesium sulphate during management of life-threatening asthma

Prevention/Promotion

- Early screening and treatment
- Appropriate dosing of magnesium containing medications

Signs and symptoms

- Reduced level of activity
- General hypotonia
- Respiratory depression with apnoea in severe cases

Investigations

- RBS
- FBC, Blood culture and urinalysis
- Cranial USS, cardiac echo, renal and KUB USS
- Electrolytes and CMP

Differential diagnosis

- Neuromuscular junction disorders: Transient acquired neonatal myasthenia , congenital myasthenia, aminoglycoside toxicity and infantile botulism
- Anterior horn cell disorders: Acute infantile spinal muscular atrophy, traumatic myelopathy, hypoxic- ischaemic myelopathy, arthrogryposis multiplex congenita
- Congenital motor or sensory neuropathies: Charcot–Marie–Tooth disease, congenital hypomyelinating neuropathy
- Congenital myopathies
- Muscular dystrophies: e.g. Duchenne and Becker muscular dystrophy
- Inborn errors of Metabolic disorders

Management

Primary level Manage ABCDE and refer
Secondary level See the tertiary-level guidance below
Tertiary level • Thorough history and examination • History of magnesium sulphate administration in a child or maternal use for eclampsia • Supportive treatment and close monitoring ABCDE approach

Follow up

- Follow up in general clinic or nursery for neonates after 2 weeks

Phosphate

Normal ranges of phosphate in the body varies with age

0 to 3 months of age: 4.8 to 7.4 mg/dL (1.55 to 2.39mmol/L)
1 to 5 years of age: 4.5 to 6.5 mg/dL (1.45 to 2.1mmol/L)
6 to 12 years of age: 3.6 to 5.8 mg/dL (1.16 to 1.87mmol/L)
13 to 20 years of age: 2.3 to 4.5 mg/dL (0.74 to 1.45mmol/L)

Hyperphosphataemia

Definition

It is a clinical condition characterised by increased serum phosphate levels above normal levels. See ranges above.

Causes/risk factors

- Excess intake of phosphate:
  - Infants fed cow's milk or formula with high phosphate levels
  - Use of phosphate enemas
- CKD with phosphate retention
- Tumour lysis syndrome
- Hypophosphatemia associated with hypocalcaemia

Promotion

- Early screening and treatment
- Adequate pre-hydration of children with malignancies at risk of tumor lysis syndrome
- Promote breastfeeding
- Avoid use of cow's milk products in early infant feeding.

Signs and symptoms

- Hypomagnesaemia leads to secondary hypocalcaemia result into tetany and/or seizures. See signs and symptoms of hypocalcaemia
- AKI due to calcium phosphate deposition in the renal tubules. See signs and symptoms of AKI
- Cardiac arrhythmia; due to calcium deposits in the cardiac conducting system
- In children with CKD, hyperphosphataemia and hypocalcaemia occur when the GFR falls below 30 mL/min per 1.73 m2 (stage G4 disease and beyond), (See signs and symptoms of CKD).

Investigations

- Exclude hypoglycaemia: RBS
- Exclude infections: FBC, MPs, blood culture, urine culture and lumbar puncture
- Serum electrolytes + CMP
- ECG + Cardiac echo

Differential diagnosis

- Hypoglycaemia
- Sepsis/ meningitis
- Hypocalcaemia
- CKD
- Tumour lysis syndrome

Management

Primary level

Assess the patient and refer

Secondary level

- Assess the patient
- Start initial investigations
- Provide supportive treatment and refer when stable

Tertiary level

- Assess the patient
- Start initial investigations
- Start treatment of hyperphosphataemia
  - Low phosphate diet, consult a dietician
  - Calcium-containing phosphate binders can be used if there is associated hypocalcaemia (calcium carbonate, calcium acetate, calcium gluconate)
  - If hyperphosphataemia is not associated with hypocalcaemia use sevelamer carbonate

Do not use the following phosphate binders in patients with CKD:

Aluminium hydroxide can cause aluminium bone toxicity

Magnesium-containing antacids e.g. magnesium hydroxide can cause hypermagnesaemia and diarrhoea.

- Involve dieticians

Consult paediatric haem-oncologists, nephrologists, endocrinologist.

Follow-up

- Follow-up in general clinic in 1 month
- Follow-up in renal clinic if presenting with CKD in 1 months

- Follow-up in Haem-onc clinic if present with tumour lysis syndrome (as advised by the oncology team, if available)

Hypophosphataemia

Definition

Clinical condition characterised by physiological reduction of serum or plasma concentration in circulation. See normal ranges above.

Causes/Risk factors

- Hereditary hypophosphataemic rickets: X-linked hypophosphataemic rickets (XLHR), autosomal dominant or recessive hypophosphataemic rickets
- Hypophosphatemia with hypercalciuria: Hereditary hypophosphataemic rickets with hypercalciuria (HHRH)
- Acquired disorder: Tumour-induced osteomalacia (TIO)

Prevention/ Promotion

- Early screening and treatment

Signs and symptoms

- Presentation is based on the underlying clinical condition:

  X-linked hypophosphataemic rickets:
  - Musculoskeletal abnormalities seen soon after birth when the infant starts weight-bearing there is evidence of hypophosphataemia, slow growth, rickets and osteomalacia

  Autosomal dominant hypophosphataemia rickets (ADHR):
  - Clinical course is similar to XLHR, however, ADHR is especially notable for its variable age of onset and incomplete penetrance.
  - The disease starts at 1-3 years of age with evident phosphate wasting, rickets, and lower extremity deformities

  Autosomal recessive hypophosphataemia rickets (ARHR):
  - Presentation similar to XLHR
  - ARHR1, 2 and 3.
  - ARHR 2 can present with hearing loss

  Hypophosphatemia with hypercalciuria:
  - Hereditary hypophosphataemic hypercalciuria rickets (HHHR): Disease onset is in childhood and presents with rickets and/or osteomalacia that is associated with hypophosphatemia, short stature, and secondary absorptive hypercalciuria

- Dent disease: Proximal tubular solute wasting, hypercalciuria, nephrocalcinosis, kidney stones, renal failure, and, in some cases, rickets
- Idiopathic hypercalciuria: Risk factor for kidney stone formation, mild hypophosphatemia and elevated levels of calcitriol

Tumour-induced osteomalacia (TIO):

- Clinical features of rickets, including gait disturbances, growth retardation, and skeletal deformities

Differential diagnosis

- See underlying conditions in signs and symptoms above

Investigations

- Serum electrolytes + CMP
- CXR looking for signs of rickets
- X-rays of the wrist bones and long bones looking for signs of rickets
- Serum PTH and vitamin D levels
- Genetic tests (if available)

Management

Primary level

Stabilise the patient and refer

Secondary level

- Start initial investigations
- Stabilise the patient and refer

Tertiary level

- Assess the patient
- Start investigations
- Start management
  - Oral phosphate 40 mg of elemental phosphorus/kg per day.
  - Vitamin D 10 to 20 ng/kg per dose, twice daily (20 to 40 ng/kg/day).
  - Add calcimimetics to prevent secondary hyperparathyroidism e.g. cinacalcet.
- Involve a dietician
- Consult paediatric nephrologist, haem-oncologist, paediatric (genetics if available)

Follow-up

- Follow-up in general clinic in 1 month
- Follow-up in renal clinic if the patient has kidney disease in 1 month
- Follow-up in haemato-onco clinic if the patient has a tumour

Renal replacement therapy (RRT)

Definition

- It is the treatment directed towards removal of toxins, metabolites, and water from the body if kidney function is transiently or persistently lost.
- Therapy can also be used in cases of poisoning or overdose.

Indications

- Various causes of AKI and uraemic symptoms (see causes of AKI)
- Various causes of CKD (see causes of CKD)
- Complications due to medical management
  - Refractory fluid overload
  - Electrolyte imbalances
  - Acid-base disturbances
- Acute poisoning e.g. by ethylene glycol, etc. (see management of acute poisoning)

Modalities of RRT

- Three main modalities used to replace renal function:
  - Dialysis (either peritoneal dialysis or haemodialysis
  - Haemofiltration
  - Kidney transplantation

Prevention/ Promotion

- Advocate for training of health workers to become certified providers of RRT
- Avoid nephrotoxic medications and adjust medications accordingly.

Contact nephrologist and/or a pharmacist for all medication dosing and if clinical management may affect or be affected by RRT

- Discuss with nephrologist on vaccination requirements for the patient
  - Patients are likely to be vaccine non-responders; additional and/or higher doses and serological testing may be needed
  - Avoid live vaccines in immunosuppressed patients.
- Avoid unnecessary blood transfusions

A. Peritoneal Dialysis (PD)

Basic Principles of peritoneal dialysis

- PD is the RRT modality that uses diffusion and ultrafiltration to remove solutes and water from the blood across the peritoneum that acts as a semipermeable membrane
- The decision to manage the patient with peritoneal dialysis should be made in conjunction with paediatrician and a paediatric nephrologist
- The Patient and guardians need to be given enough information and education before initiation of RRT
- Signed informed consent should be obtained.

Procedures in PD

- Peritoneal catheter placement
  - Consult paediatric urology/paediatric surgical team/any trained health personnel for PD catheter placement
  - The peritoneal catheter is inserted into the peritoneal cavity and tunnelled to an exit site (anti-septic procedure)
- Initiation of dialysis
  - Dialysate is infused into the abdominal cavity and left for a set period of time (dwell time) to allow diffusion
  - The dialysate draws water and electrolytes/waste products across the peritoneal membrane
  - The fluid in the abdominal cavity (effluent) is removed at the end of the dwell time

Complications of peritoneal dialysis

- Metabolic disturbances: weight gain, hyperglycaemia
- Infections e.g. exit site and catheter tunnel infections
- Peritoneal dialysis-associated peritonitis
- Protein loss: hypoalbuminaemia
- Abdominal hernias: umbilical and inguinal hernias are most common
- Leakage of dialysate
- Pleural effusion - rare
- Catheter blockage

Frequently examine the peritoneal dialysis catheter and exit site for signs of infection. Signs of infection include swelling and erythema around the catheter tunnel and exit site and purulent/ pus drainage at the exit site. Consider ultrasound for a more detailed assessment if infection is suspected.

Peritoneal dialysis-associated peritonitis

Definition
Peritonitis arising as a complication of peritoneal dialysis.

Risk factors
- Peritoneal dialysis being performed in an unclean environment, inadequate peritoneal dialysis training
- Invasive procedures performed during dialysis e.g. colonoscopy, cholecystectomy
- Patient factors include hypoalbuminaemia, Staphylococcus aureus nasal carriage, previous exit site infection

Prevention
- Antibiotic prophylaxis prior to insertion of the peritoneal dialysis catheter
- Systemic prophylaxis prior to certain invasive procedures e.g. dental procedures, invasive abdominal procedures etc.
- Daily application of topical antibiotics to the catheter exit site
- Health care providers and patient education on peritoneal dialysis catheter care
    - Keeping the exit site clean
    - Practicing thorough hand hygiene prior to dialysis exchange
    - Prompt treatment of exit site infections
    - Addressing modifiable risk factors
- Monitor effluent dialysis fluid characteristics when draining after dwell time

Signs and symptoms
- Mostly asymptomatic and identified by cloudy peritoneal effluent
- Clinical features of peritonitis include abdominal pain, distension, and fever on physical examination the patient may have rebound tenderness, rigidity, and guarding. (See management of Acute Abdomen – Peritonitis)

Investigations
- Collect a peritoneal fluid sample for microscopy, culture and sensitivity (MCS).
- If the effluent is cloudy, initiate empiric antibiotic therapy.

Start empiric antibiotic therapy for presumed peritonitis in all patients with cloudy peritoneal effluent, even if they are asymptomatic.

- Systemic signs of infection: Initiate diagnostic work-up for sepsis.
- Confirm peritonitis if ≥ 2 of the following are present:
  - Clinical features of peritonitis
  - Peritoneal fluid with > 100 WBCs/mcL (typically > 50% polymorphonuclear cells)
  - Positive peritoneal fluid culture

Management

Tertiary level

- Admit the patient to isolated high-dependence unit (HDU) if available
- Start management and treatment for sepsis if clinical features are suggestive of sepsis (see management of sepsis) including empiric systemic antibiotics.
- If the patient presents with no systemic signs of infection
  - Consult nephrology and infectious diseases specialists if available
  - Initiate broad-spectrum empiric intraperitoneal antibiotics
  - Adjust the dose based on renal function as per hospital protocol
  - Recommended regimens include Vancomycin or cephalosporin e.g. ceftriaxone (gram- positive cover) or aminoglycoside (gram-negative cover)
  - Adjust antibiotics based on culture and susceptibility results
- Start antifungal prophylaxis (oral nystatin or fluconazole)
- Provide supportive treatment as needed e.g. oxygen therapy, pain management, antiemetics etc.
- Patients with relapsing or refractory peritonitis or confirmed fungal peritonitis: Consider removal of the peritoneal dialysis catheter and advocate for temporary haemodialysis
- Involve the palliative care team
- Involve the renal dietician in the management of patients with renal disease requiring dialysis

B. Haemodialysis

- Not routinely recommended or performed in Malawian paediatric patients
- Adolescent patients transitioning to adult care can be considered
- Discuss all patients requiring dialysis with a nephrologist

Basic principles

- Haemodialysis uses diffusion and ultrafiltration to remove solutes and water from the blood

- More effective at removing small molecules (e.g., urea, creatinine, ammonia) than larger molecules
- Blood is pumped through the dialysis unit on one side of a semipermeable membrane and dialysate in the opposite direction on the other side of the membrane
- Molecules diffuse across the semipermeable membrane down their concentration gradient

Procedure

- Intermittent renal replacement therapy (RRT)
  - Occurs over 3–5 hours; may be prolonged as per patient requirement lasting 6–18 hours (prolonged intermittent renal replacement therapy)
  - Most common option for outpatient administration in patients with CKD but it can also be used for acute RRT
- Continuous renal replacement therapy
  - Gradual fluid and solute clearance over 24 hours
  - Used almost exclusively for acute RRT
  - Preferred if fluid shifts are contraindicated

Complications of haemodialysis

<u>Venous Access complications:</u>

- Loss of access due to thrombosis or stenosis
- Infections e.g. skin and soft tissue infection, central line-associated bloodstream infection
- Local aneurysm
- AV access steal syndrome: Painful ischaemia of the hand secondary to the AV fistula or graft shunting blood away from the distal limb
- Dialysis vascular access haemorrhage
  - Apply firm pressure for 15–20 minutes; avoid occluding the vessel
  - If the patient is haemodynamically unstable:
  - Manage as haemorrhagic shock
  - Place tourniquets above and below the site and attempt a figure of 8 or purse-string
  - suture
  - Determine time of last dialysis and consider anticoagulant reversal
  - Urgently consult vascular surgery if bleeding is heavy, persists, or recurs.

<u>Cardiovascular complications:</u>

- Hypotension and heart failure
- Increased bleeding risk caused by platelet dysfunction due to CKD and/or

platelet contact with the dialysis membrane. Avoid systemic anticoagulation solely to maintain or improve haemodialysis catheter patency.

Dialysis disequilibrium syndrome:

- It is a clinical syndrome characterised by development of acute cerebral oedema secondary to the rapid extraction of osmotically active substances e.g. urea, NaCl from the blood.

Other complications:

- Acquired cystic kidney disease
- Cramps
- Electrolyte abnormalities e.g. hypophosphatemia
- Dialysis-related amyloidosis, which can cause carpal tunnel syndrome
- Allergic reaction to the equipment or dialysate

C. Renal transplant

- Not routinely recommended or performed in Malawian paediatric patients
- Discuss all patients who can benefit from renal transplantation with a nephrologist
- Renal transplant cases will be discussed at external referral meetings where the final decision is made
- Involve renal dietician and palliative care team

Indications

- All patients with End Stage Renal Disease (ESRD) can benefit from renal transplant

Contraindications

Absolute:

- Unsuitable vascular anatomy
- Aorto-bifemoral bypass or an aorto-iliac stent graft that extends to both external iliac arteries
- Circumferential calcification of the iliac vessels
- Thrombosis of the iliac vein and inferior vena cava
- Active infection (e.g. tuberculosis, invasive fungal infections, osteomyelitis)
- Malignancy in the past 2 years
- Obesity
- Lack of adequate social support (e.g. patient in a nursing home, homeless patient) Relative:

- Age < 1 year or > 75 years
- Diseases of the lower urinary tract
- For female paediatric patients in reproductive age range, pregnancy is a contraindication
- Psychiatric diseases or psychosocial problems
- Systemic diseases potentially leading to kidney damage
- Proteinuria > 300 mg/day
- Hypertension that does not respond to treatment
- Diabetes mellitus

Hypertension

Definition

- Hypertension (HTN) is the increase of systolic or diastolic blood pressure above the 95th percentile for age, gender and height
- Several HTN categories have been developed to classify HTN according to the national population.
- Below is the table of 2017 American Academy of Paediatrics (AAP) updated definitions for paediatric blood pressure categories which is widely used for reference in many countries.

2017 American Academy of Paediatrics updated definitions for paediatric blood pressure categories

	For children 1 to <13 years	For children ≥13 years
Normal BP	Systolic and diastolic BP <90th percentile	Systolic BP <120 and diastolic BP <80 mmHg
Elevated BP	Systolic and diastolic BP ≥90th percentile to <95th percentile, **OR** 120/80 mmHg to <95th percentile (whichever is lower)	Systolic BP 120 to 129 and diastolic BP <80 mmHg
Stage 1 HTN	Systolic and diastolic BP ≥95th percentile to <95th percentile+12 mmHg, **OR** 130/80 to 139/89 mmHg (whichever is lower)	130/80 to 139/89 mmHg
Stage 2 HTN	Systolic and diastolic BP ≥95th percentile+12 mmHg, **OR** ≥140/90 mmHg (whichever is lower)	140/90 mmHg

- Paediatric HTN is further classified into primary and secondary HTN, where primary HTN there is no identifiable cause whilst in secondary HTN the underlying cause is identified
- Another classification which is based on ambulatory BP monitoring. This classification classifies BP into white coat HTN and masked HTN
    - White coat HTN or Office HTN is an isolated BP ≥95 percentile for age and

sex determined within clinical setting but normal values outside the clinical settings

- Masked HTN is characterised as normal BP in clinical or office setting but a high ambulatory BP outside the clinical setting. Mostly commonly, it is associated with obesity and increased left ventricular load, which are all risk factors for early adult cardiovascular disease

Risk factors

Modifiable risk factors

- Obesity
- Increased dietary sodium intake
- Obstructive sleep apnoea (OSA)
- Decreased physical activity
- Breast feeding is protective. Studies indicate that breastfeeding lowers BPs in childhood posing greater risk of developing HTN in those children who were never breastfed.
- Tobacco exposure
- Adverse childhood experiences (ACEs): traumatic events in childhood, abuse, neglect, parental mental health problems and household dysfunction increase the risk of overweight and obesity (in Malawi it may depend on social background), cardiovascular disease (coronary heart disease and stroke) and HTN. The ACEs are associated with increase mortality and morbidity
- Prenatal and neonatal factors e.g. low birth weight and in utero exposure to pre-eclampsia has been associated with the development of primary HTN

Non-modifiable factors

- Sex: increased risk of developing HTN is seen more in boys than in girls
- Family history of HTN mostly seen in patients with primary HTN
- Race and ethnicity – there is increased risk shown in Black and Hispanic children compared with White and Asian children in studies done in United States

Causes

Primary HTN

- There is no underlying cause identified.
- This is a diagnosis of exclusion

Secondary HTN

- There is an identifiable underlying cause identified.
- The identified disorder can be curable with complete resolution of HTN

Causes of secondary HTN in children and adolescents

Kidney disease • Pyelonephritis • Kidney parenchymal disease • Congenital anomalies • Reflux nephropathy • Acute glomerulonephritis • IgA Vasculitis (Henoch-Schönlein purpura) • Kidney trauma • Hydronephrosis • Haemolytic uraemic syndrome • Kidney stones • Nephrotic syndrome • Wilms' tumour • Hypoplastic kidney • Polycystic kidney disease	**Pharmacologic causes** • Sympathomimetics • Corticosteroids • Stimulants • Oral contraceptives • Anabolic steroids • Cocaine • Phencyclidine (PCP) • Liquorice • Nicotine • Caffeine
Endocrine disease • Hyperthyroidism • Congenital adrenal hyperplasia • Cushing's syndrome • Primary aldosteronism • Primary hyperparathyroidism • Diabetes mellitus • Hypercalcemia • Pheochromocytoma	**Vascular disease** • Renal artery abnormalities • Renal vein thrombosis • Coarctation of the aorta • Patent ductus arteriosus • Arteriovenous fistula
Neurologic causes • Increased intracranial pressure • Guillain-Barré syndrome	**Psychologic causes** • Mental stress • Anxiety
Other causes • Neuroblastoma • Heavy metal poisoning • Acute pain • Collagen vascular diseases • Neurofibromatosis • Tuberous sclerosis	

Prevention/promotion

- Early enrolment into antenatal care services to avoid complications of pre-eclampsia and premature delivery
- Promote exclusive breastfeeding
- Promote healthy diet
- Reduce sedentary lifestyle
- Promote physical education in schools
- Increase community screening at health posts and refer appropriately
- Early identification and treatment by advocating for supplying appropriately sized cuffs for all age groups, including neonates in the health facilities.
- Early identification and treating of all conditions that are associated with HTN
- Discourage indoor smoking
- Health promotion messages targeting teenagers who are at risk of indulging in risky behaviours such as smoking and drinking which can predispose them to early development of HTN and cardiovascular diseases

Signs and symptoms

- Can be asymptomatic only detected on a hospital consultation
- Non-specific hypertension symptoms
    - Headaches (early morning or waking up headache), dizziness, tinnitus, blurred vision, flushed appearance, epistaxis, chest discomfort, heart palpitations, nervousness, fatigue, sleep disturbance
    - Bounding pulses on palpation
- Symptoms of underlying disease
- Suspect secondary hypertension in the following:
    - Severe hypertension
    - Resistant hypertension
    - Target organ damage disproportionate to the degree of hypertension
    - Hypertensive emergency
- Unusual onset of hypertension especially in all children and adolescent patients
- Drug induced hypertension
- Unprovoked or significant hypokalaemia

Signs and Symptoms	Possible cause of hypertension
CNS: History of Head Trauma, headache, visual disturbance, lethargy, seizures, tremors, morning vomiting	Elevated intracranial pressure
Hearing: Hearing loss	Renal disease (e.g. Alport syndrome) Lead poisoning

Cardiovascular: Palpitations, irregular pulse	Catecholamine excess
Renal: Oedema, history of UTI or unexplained fever, abnormal urine colour, enuresis, flank pain, dysuria	Renal disease or condition (e.g., pyelonephritis, acute glomerulonephritis, acute kidney injury, and chronic kidney disease)
Skin: Rash, sweating, pallor	Catecholamine excess Thyroid dysfunction Renal vasculitis
Recent medical history: Recent pharyngitis or impetigo, exposure to sources of enterohemorrhagic E. coli	Post-infectious glomerulonephritis Haemolytic uremic syndrome
Medications: Sympathomimetics, oral contraceptives, corticosteroids	Side effect of medication
Substance use: Cocaine, amphetamines, anabolic steroids, phencyclidine, ephedra- containing alternative medications, caffeine	Drug-mediated effects
Family history: Hypertension, early MI, diabetes, stroke	Essential hypertension
Sexual history: Postmenarchal female actively engaged in sexual intercourse	Preeclampsia
Neonatal history: Use of umbilical artery catheters	Renovascular hypertension
Growth history: Excessive weight gain or loss, change in growth percentiles	Obesity, thyroid dysfunction
Dietary history: Types and amount of food ingested; salt craving	Obesity, essential hypertension
Social history: Stress factors at home and school	Stress

Distinguishing clinical features between primary (essential) and secondary pediatric hypertension

Clinical features	Primary HTN	Secondary HTN
Age:		
Prepubertal		Secondary HTN is more likely in younger children, especially those less than six years of age
Postpubertal	Older children and adolescents are more likely to have primary HTN	
Diastolic HTN		Diastolic HTN is more likely to be associated with secondary HTN
Nocturnal HTN		Nocturnal HTN is more likely to be associated with secondary HTN
Overweight/obesity	Overweight or obese children/ adolescents are more likely to have primary HTN	
Family history of HTN	Children with a positive family history of primary HTN are more likely to have primary HTN.	Family history may be positive in some cases of secondary HTN due to a monogenic cause (e.g., autosomal dominant polycystic kidney disease)
Symptoms of underlying disorder	Patients with primary HTN are typically asymptomatic.	Patients with secondary HTN often have other symptoms related to the underlying cause (e.g., headache, sweating, and tachycardia due to

		catecholamine excess in patients with pheochromocytoma)

Promotion/prevention

- Early screening and detection
- Advocate for community blood pressure screening e.g. at the market centres, churches and other public functions
- Advocate for screening of hypertension during all hospital consultations
- Advocate for 4 limb blood pressure measurement
- Advocate for screening of secondary hypertension causes in all children presenting with elevated blood pressures

Investigations

- The main goal of doing extensive investigation is to:
- Differentiate between primary and secondary HTN.
- Identify any treatable condition contributing to HTN. See table on causes.
- Identify other comorbid conditions or risk factors for early cardiovascular disease (CVSD).
- Serum urea and creatinine to assess for possible renal disease causing HTN
- Serum electrolytes and blood gas analysis - hypokalaemia and metabolic alkalosis indicate excess mineralocorticoids (e.g. aldosterone) secretion.
- Do serum renin and aldosterone level, if available, to confirm mineralocorticoid excess.
    - Examples of excess mineralocorticoid secretion disorders include Congenital Adrenal pseudohypoaldosteronism (Gordon syndrome) etc.
- CMP
- Urinalysis
    - To assess if there is renal disease
    - Glucosuria may be suggestive of diabetes mellitus
- Lipid profile to look for dyslipidaemia. In obese children do the following additional tests
    - Haemoglobin A1c, fasting blood glucose to exclude diabetes mellitus
    - Serum alanine transaminase to screen for fatty liver disease
- Plasma and urine catecholamines – catecholamine excess as seen in Pheochromocytoma and neuroblastoma.
- Kidney ultrasound- recommended in all patients with HTN.
    - Kidney ultrasound – looks for presence of structural abnormalities or abnormally small kidney size which may indicate scarring.

    - If kidney ultrasound is suggests of renal scarring do Dimercaptosuccinic acid (DMSA) scan if available.
- Renovascular imaging
    - Standard digital subtraction angiography (DSA) previously called renal angiography is gold standard for investigating renovascular diseases in children
    - Magnetic resonance angiography (MRA) AND computed tomography angiography can be used.
    - Duplex doppler can be used if the above are not available but has low sensitivity.
    - Indicated in patients with predisposing factors or findings associated with renal artery stenosis e.g. prior umbilical artery catheter placements, family history or findings for neurofibromatosis, an abdominal bruit, or a significant size discrepancy on renal ultrasonography
- Cardiac echo – Left ventricular hypertrophy (LVH) is common end organ damage from HTN and can be detected on a cardiac echo
- Sleep study in OSA
- Drug screening e.g. cocaine, methamphetamine

A: Management of chronic hypertension in children and adolescents

- The target BP goal for children diagnosed with hypertension treated with non-pharmacologic and/ or pharmacologic therapy is a reduction of systolic and diastolic BP below the 90th percentile for age and sex or <130/80 in adolescents 13 years or older
- Screen all patients for cardiovascular disease risk factors and treat as necessary.

Primary level

- Refer all suspected cases of hypertension to secondary level for further management

Secondary level

- Screen all cases for HTN
- Screen all cases of HTN for possible non-complicated causes of secondary HTN and start treatment
- Confirm the diagnosis of HTN and start treatment

Non-pharmacological management of hypertension

- Lifestyle modification
- Weight loss in obese patients - maintain BMI < 25 kg/m2.
- Restrict salt with increased potassium intake from fresh fruits and vegetables involve the dietician

- Dietician's advice recommended.
- Reduce alcohol intake & stop smoking.
- Follow a healthy eating plan i.e. low fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables. Involve dietician if available.
- Regular moderate aerobic exercise, e.g. 40 minutes brisk walking at least 3 times a week.

Pharmacological management of chronic hypertension for infants, children, and adolescents:

- Antihypertensive drugs for outpatient management of chronic hypertension for infants, children,
  and adolescents
- First line treatment with ACE inhibitors (ACEI) or Angiotensin receptor blockers (ARBs) or Calcium
  - channel blockers (CCB)
  - Calcium Channel Blockers
    - Nifedipine 0.25mg/kg BD increase to QID if no response maximum dose 1mg/kg/day.

- Refer and discuss all suspected cases with complicated primary or secondary HTN
- Refer and discuss all cases with acute severe HTN to tertiary level

Follow up all cases of HTN in NCD / General clinic

Tertiary level

- Screen all patients for HTN and investigate for secondary causes.
- Confirm the diagnosis of HTN and start treatment
- Manage all cases referred with acute severe hypertension

Non-pharmacological management of hypertension

- See Secondary Level above.

Pharmacological management of chronic hypertension for infants, children, and adolescents:

- Antihypertensive drugs for outpatient management of
- First line treatment with ACE inhibitors (ACEI) or Angiotensin receptor blockers (ARBs) or Calcium
  channel blockers (CCB)
  - Calcium Channel Blockers
    - Nifedipine 0.25mg/kg BD increase to QID if no response maximum

dose 1mg/
kg/day.
- Amlodipine 0.05 to 0.2mg/kg od.

- ACE inhibitors
  - Enalapril dose infant ≥ I month of age 0.08mg/kg/day; children 0.1
  - mg/kg/day (maximum 40mg) daily to twice a day.
  - Captopril dose infants 0.05mg/kg/dose daily to 4 times a day; children 0.05mg/kg/dose (maximum 6mg/kg) three times a day.
  - Contraindications: Pregnancy, angioedema.
  - Common adverse effects: Cough, headache, dizziness, asthenia.
  - Severe adverse effects: Hyperkalaemia, acute kidney injury, angioedema, fetal toxicity.
- ARBs
  - Losartan dose > 6 years old 0.7mg/kg (maximum 50mg) daily
  - Candesartan dose 1 to 5 years old 0.02mg/kg/day (maximum 4mg/day) daily or twice a day. <50kg 4 mg per day

- If target BPs not achieved add Thiazide diuretics
- **Other management considerations:**

Stage 1 primary hypertension (HTN) without evidence of end-organ damage or CVD risk factors

- Non-pharmacologic therapy is the initial intervention.
- If BP target goals are not met within four to six months after initial therapy (ie, BP below the 90th percentile), pharmacologic therapy is initiated.

Stage 2 primary HTN

- Treat with both non-pharmacologic and pharmacologic therapy.
- Patients with stage 2 HTN and neurologic symptoms including headache, mental status changes, and neurologic findings should be emergently evaluated and treated

Secondary HTN

- Start to treat underlying cause if treating the cause is adequate to treat HTN.
- If treating underlying cause does not treat hypertension, start pharmacologic and non- pharmacologic therapy dependent on the elevation of BP

HTN with Chronic kidney disease (CKD)

- Start both non-pharmacologic and pharmacologic therapy

Diabetes mellitus (DM) patients with HTN

- Start both non-pharmacologic and pharmacologic therapy.
- Involve paediatric nephrologist, endocrinologist, paediatric cardiologist, Paediatric oncologists,
- Paediatric surgeons and other needed specialised care as indicated
- Involve allied medical departments as indicated e.g. physiotherapy, palliative care, psychosocial support etc.

B: Management of acute severe hypertension

Definitions

Hypertensive emergency: An acute severe elevated BP (above the level of stage 2 hypertension) with evidence of life-threatening symptoms or target-organ damage e.g. hypertensive encephalopathy, heart failure, or acute kidney injury.

Hypertensive urgency: An acute severe elevation in BP without life-threatening symptoms
or evidence of acute target-organ damage.

Note: Symptoms or target organ damage is more important than the absolute BP level!!

For example, a child with chronic hypertension with very high BP measurements without symptoms. Another child with an acute moderately high in BP with hypertensive emergency because the child has symptomatic or has signs of end organ damage.

Management

Primary level
- Manage ABCDE
- Refer all patients

Secondary level

- Manage ABCDE
- Give supportive oxygen therapy
- Stop all medications that lead to hypertension
- Manage the hypertension:
  - Start hydralazine 0.1 to 0.2 mg/kg/dose every 4 to 6 hours, titrate as needed in consultation with paediatricians
  - If hydralazine is not available, give nifedipine 0.25mg/kg PO
  - **Target BP systolic at 95th percentile for age and sex**

Short-acting oral nifedipine is not recommended in children due to difficulties with dosing,
prolonged and unpredictable action, risk of hypotension, and re-bound hypertension.

The onset of action for other calcium channel blockers is too slow to recommend them for children with hypertensive urgencies.

- Provide continuous cardiorespiratory monitoring, plus pulse oximetry and ECG monitoring if available.
- Treat seizures with anticonvulsants (see management of seizures)

Tertiary level

- Provide continuous cardiorespiratory monitoring, plus pulse oximetry and ECG monitoring if available.
- Stop all medications that can lead to hypertension
- Place 2 IV lines. One for administration of antihypertensive drugs, the other one for general use
- Treat seizures with anticonvulsants (see management of seizures)
- Start IV antihypertensive medications

Hypertensive emergency

- Start labetalol bolus 0.2 to 1 mg/kg/dose (maximum dose: 40 mg/dose) **then**
- Labetalol IV infusion (0.25 to 3 mg/kg/hour) or repeated as boluses every 10 minutes until
- the desired BP is reached
- Start with the lower dose and titrate upwards according to response
- Target BP systolic at 95th percentile for age and sex

or

- Start nicardipine 0.5 to 1 mcg/kg/minute continuous IV infusion or
- Nicardipine boluses 30 mcg/kg (up to 2 mg) of until the desired BP is reached.

- Start with the lower dose and titrate upwards

If no response to initial treatment above within 30 minutes:

- Start continuous IV infusion of both labetalol and nicardipine
- Alternative drugs include hydralazine and sodium nitroprusside have adverse effects that make them less suitable for the initial treatment of severe hypertension in children
- Start hydralazine 0.1 to 0.2 mg/kg/dose (maximum dose: 20 mg/dose) every 4 to 6 hours, titrate as needed OR
- Start Sodium nitroprusside 0.3 - 0.5 mcg/kg/minute titrate every 5 minutes to desired effect (maximum dose 10 mcg/kg/minute). Severe side effect is cyanide toxicity.

Do not lower the BP by more than 25 percent of the planned BP in the first eight hours of treatment in patients with chronic hypertension.
This will cause irreversible target-organ damage, including permanent neurologic sequelae, visual defects, myocardial infarction, and renal insufficiency. This is because of abnormal autoregulatory responses in circulatory beds of these organs.

Hypertensive urgency

- Target BP <90th percentile for age, sex and height
- Start labetalol IV bolus (preferred), or
- Start hydralazine or nicardipine IV bolus

Management of chronic condition with hypertensive urgency

- Do not lower BPs quickly
- Give oral medications if can take medications orally. If the patient cannot take oral medications:
- Give IV labetalol bolus doses (preferred)
- In infants < 1 year of age or for children with asthma, give IV doses of hydralazine or nicardipine (give slowly to lower the BP)
- Treat any associated conditions appropriately e.g. pulmonary oedema. See management of heart failure in children.
- Monitor BP and other vital signs regularly
- If there is papilloedema, altered mental status, seizures, or neurologic deficits on physical examination, request a CT scan or MRI if available
- Discuss the case with seniors/paediatrician/nephrologist/endocrinologist i.e.

people with expertise in managing HTN in children

Follow-up

- Follow up in PEN-Plus clinic in 1 month
- Conduct regular patient education on non-pharmacological management of hypertension in the clinic
- Perform regular blood tests to assess for end-organ damage
- Schedule regular fundoscopy to assess for end-organ damage in the eyes
- Collaborate with allied medical departments needed for the management of hypertension e.g. physiotherapy for stroke patient secondary to HTN, psychosocial support services if available, palliative care etc. Avoid haemolysis when acquiring blood sample for potassium assessment

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