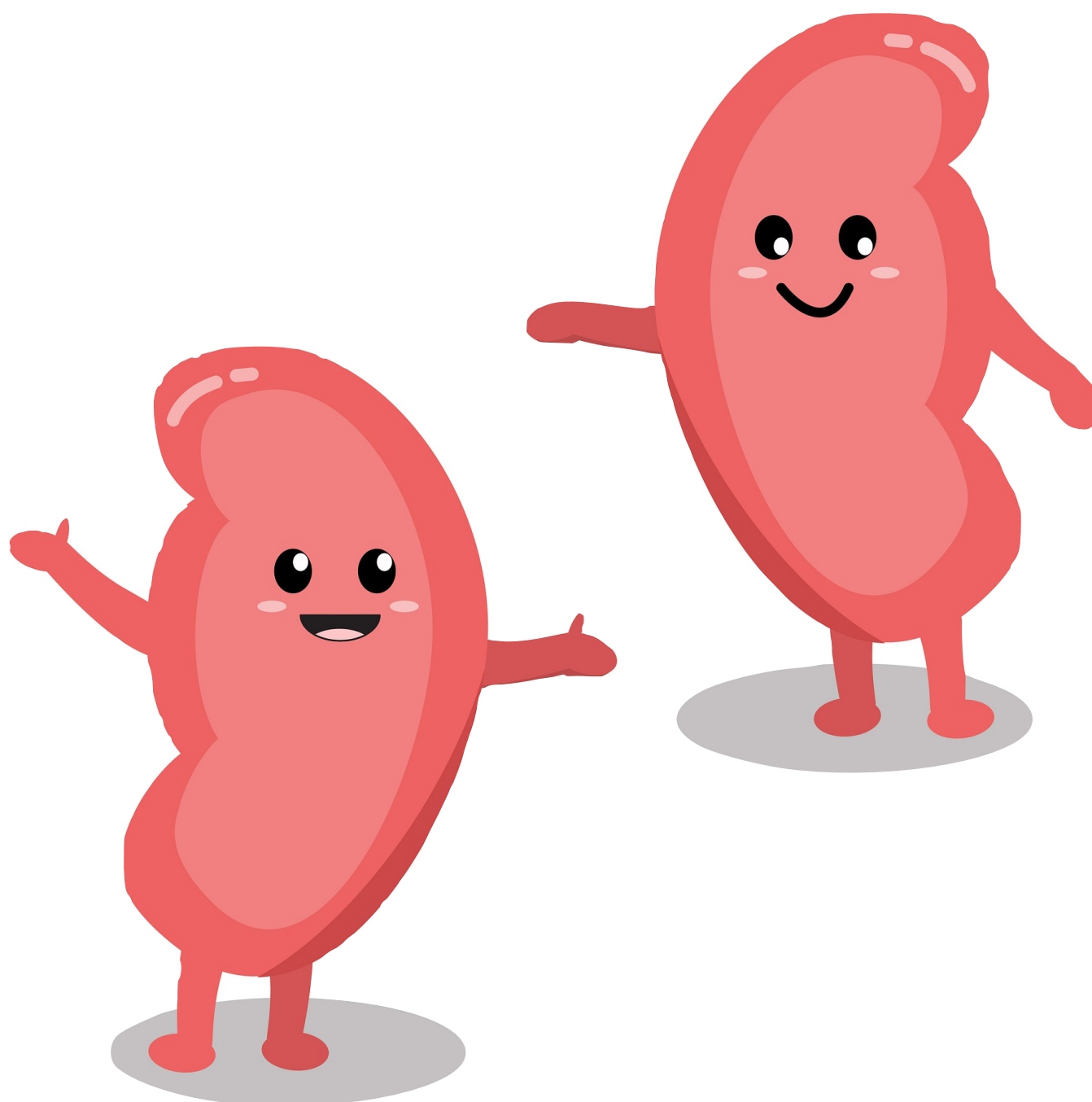


PAEDIATRIC NEPHROLOGY RESIDENT HANDBOOK

FIRST EDITION



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2021



**CANADIAN ASSOCIATION OF
PAEDIATRIC NEPHROLOGISTS**

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- Kidney Cover - Suzakar (page 0)

INTRODUCTION

Welcome to your paediatric nephrology rotation! Kidneys are arguably one of the most important (if not *the* most important!) organs in our body and have many integral functions – management of fluid balance, acid-base homeostasis, electrolytes, toxin/waste removal, blood pressure regulation, bone health, anemia, growth and more! A basic understanding of kidney disease and manifestations in children is crucial as a general paediatrician.

We hope you will find this handbook a helpful guide to key concepts in renal physiology and the clinical practice of paediatric nephrology.

We are interested in your feedback on the guide – please email paednephrohandbook@gmail.com with any comments or questions. If you would like to provide any feedback anonymously, please visit the following link: <https://shorturl.at/ikDE5> or QR code below.



This handbook will be revised and updated every 3 years, to ensure the content is up to date.

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1

SECTION 1

Foundations of Paediatric Nephrology

OUTLINE

1. History & Physical Exam
2. Diagnostic Tests
3. Kidney Development
4. Fluids and Electrolytes

Abbreviations

ABC = airway breathing circulation
 ADH = antidiuretic hormone
 ADPKD = autosomal dominant polycystic kidney disease
 AKI = acute kidney injury
 ARPKD = autosomal recessive polycystic kidney disease
 BMI = body mass index
 BSA = body surface area
 C/S = Cesarean section
 CFU = colony forming units
 CKD = chronic kidney disease
 Cl = chloride
 CM = centimeter
 CNS = central nervous system
 CT = computerized tomography
 CVS = cardiovascular system
 D5W = 5% dextrose in free water
 DCT = distal convoluted tubule
 DKA = diabetic ketoacidosis
 DMSA = dimercapto succinic acid
 DTPA = diethylenetriamine pentaacetate
 EDTA = ethylenediaminetetraacetic acid
 ECG = electrocardiogram
 ESKD = end stage kidney disease
 FWD = free water deficit
 G = gram
 GFR = glomerular filtration rate
 GI = gastrointestinal
 H = hydrogen
 H+N = head and neck
 HCO₃ = bicarbonate
 Hr = hour

IUGR = intrauterine growth restriction
 IV = intravenous
 K = potassium
 Kg = kilogram
 L = litre
 MAG = mercaptoacetyltriglycine
 mEq = milliequivalent
 mL = milliliter
 Na = sodium
 NH₄ = ammonium
 NICU = neonatal intensive care unit
 nMol = nanomole
 NPO = nil per os (nothing by mouth)
 NS = normal saline
 pCO₂ = partial pressure of carbon dioxide
 PCT: proximal convoluted tubule
 RBC = red blood cell
 RTA = renal tubular acidosis
 SIADH = syndrome of inappropriate antidiuretic hormone
 TBW = total body water
 TTKG = transtubular potassium gradient
 US = ultrasound
 UTI = urinary tract infection
 VCUG = voiding cystourethrogram
 VUR = vesicoureteric reflux
 WBC = white blood cell

1. HISTORY & PHYSICAL EXAM

HISTORY BY CHIEF COMPLAINT

Key elements of a renal-specific history are outlined below. Please remember that kidney disease can manifest in a variety of ways and sometimes can be completely asymptomatic. Therefore, the astute clinician may need to pick up on subtle signs such as poor growth, polyuria, or fatigue.

Questions to be asked when taking a general renal history might include the antenatal history, family history, growth and development, lower urinary tract symptoms, urine colour and quantity. However, more specific history questions based on chief complaint are listed below:

Concern for nephritic syndrome/glomerulonephritis (gross hematuria, hypertension, edema):

- What is the colour of the urine? Does it occur with every void? How many times has the colour changed? Ever happened before?
- Clarify if the urine is bright pink/red or tea/cola coloured, or presence of clots?
- If there is gross hematuria, is it present at the start but clears, noted at the end of the urinary stream (terminal) or throughout the whole stream?
- Any associated dysuria, abdominal/flank pain, urinary urgency, frequency, swelling/edema?
- Clarify amount of fluid intake and urine output (any changes/decrease in output)?
- Difficulty breathing
- Intercurrent illness or recent illness?
- General review of systems, including specific focus on autoimmune symptoms (associated joint pain/swelling, rashes, Raynaud's phenomenon, mouth ulcers, pleuritis)
- Medications, nephrotoxins
- Family history of autoimmune/rheumatological disease (including Lupus, vasculitis), renal disease, sensorineural hearing loss, dialysis, or kidney transplantation

Concern for proteinuria/nephrotic syndrome:

- Any swelling/edema – ask about eyelids, abdomen, peripheral limbs, scrotal/genital swelling? Any sudden weight gain? Any associated gross hematuria? Ever happened before?
- Fluid intake, and urine output?
 - *Note, parents may not equate decreased urine output being associated with their condition (as they would with dehydration/vomiting) and so this is important to clarify.
- Foamy, frothy urine?
- Any intercurrent illness?
- General review of systems
- Family history of autoimmune/rheumatological disease
- For congenital nephrotic syndrome: weight of placenta, elevated alpha-fetoprotein level during pregnancy

Concern for chronic kidney disease:

- When was the increased creatinine noted? Any history of acute kidney injury?
- Any issues with failure to thrive/poor growth, short stature, decreased appetite?
- Any fatigue? Pruritus? Nausea/vomiting?
- Any issues with bowed legs/bony deformities/fractures?
- Polyuria, polydipsia?
- Any history of UTIs?
- Medications, nephrotoxins
- Other co-morbidities (i.e. cardiac disease, CNS, developmental delay, eye manifestations)
- Previous or in-utero ultrasound findings
- Family history of renal disease, hearing loss, dialysis or transplantation

Concern for UTIs:

- History of associated dysuria, flank pain, fever, urgency, frequency, urinary hesitancy, gross hematuria
- History of sexual activity (for adolescents)
- History of constipation
- Fluid intake
- Voiding history – how often, any holding behaviour/maneuvers, nocturia, any enuresis
- Previous urine cultures (and how they were obtained: urine bag, mid-stream or catheter)
- Any antibiotic prophylaxis
- Previous ultrasound or other imaging

Concern for acute kidney injury:

- Pre-renal: any history of volume loss i.e. vomiting/diarrhea, blood loss, increased insensible losses, cardiac surgery/poor cardiac function, decreased perfusion
- Renal: nephrotoxins, sepsis, check for symptoms of glomerulonephritis, any concern for vascular thrombosis
- Post-renal: urine output, abdominal pain/distension, any history of kidney stones, any urological history, any concern for neurogenic bladder

Concern for hypertension:

- When was it noted, is the measurement technique correct (correct cuff size, while patient is calm, and seated, measured in right arm)?
- How high is the blood pressure (please see hypertension section to assess stage of hypertension)?
- Is the patient symptomatic? Headaches, chest pain, blurry vision, etc.
- CNS: any history of headaches, blurred vision, poor school performance
- CVS: difference between upper and lower limb perfusion, claudication
- H+N: symptoms of obstructive sleep apnea, i.e. any history of snoring, pauses in breathing

- Renal: history of renal disease, UTIs, glomerulonephritis etc.
- Endocrine: thyroid symptoms (headaches, tachycardia, GI symptoms, hair loss, sweating), cortisol (Cushingoid appearance, weight gain, acne, muscle weakness), pheochromocytoma (headaches, flushing, palpitations, sweating)
- Fluid intake, IV fluids, intake/output and fluid balance
- Medications/Drugs: e.g. caffeine, steroids, amphetamines
- Dietary history – salt intake, juice intake, soft drinks, any junk food, weight gain, BMI
- Physical activity – amount of time, what types of activities, time spent sedentary
- Long-term effects of hypertension: last eye exam (for hypertensive retinopathy), last echo (looking for left ventricular hypertrophy), and last renal investigations (for proteinuria, chronic kidney disease)

Concern for congenital anomalies of the kidney and urinary tract:

- Antenatal history including any pregnancy complications, ultrasound findings of the kidneys and bladder (i.e. degree of pelviectasis, bladder wall thickness, cysts, any note of pulmonary hypoplasia, or poor respiratory effort on biophysical profile), gestational age, oligohydramnios/polyhydramnios, IUGR, medications during pregnancy, illness/infection during pregnancy, maternal diabetes
- General delivery history specifically focusing on risk of respiratory distress at birth due to oligohydramnios, lung hypoplasia
- Any associated anomalies at birth/dysmorphic features? Aniridia, hemihypertrophy, ambiguous genitalia, ear anomalies, cryptorchidism, absent abdominal wall musculature?
- Urinary stream/flow, when was the first wet diaper after birth?
- Antibiotic prophylaxis being used? UTI symptoms? Enuresis? Bladder emptying? Urology follow up?

Concern for kidney stones:

- Symptoms of dysuria, gravel/sand/crystals in the urine or diaper, gross hematuria, flank pain, voiding pattern
- Has this happened before? Any history of surgical interventions (stent placement, lithotripsy, etc.)

- Tubulopathy symptoms: polyuria, polydipsia, poor growth, failure to thrive
- History of UTIs
- Amount of fluid intake
- Mobilization/physical activity
- Diet (including calcium intake to meet DRI, ketogenic diet, salt intake, protein)
- Medications including topiramate, steroids, vitamin D, furosemide
- Co-morbidities (i.e. inflammatory bowel disease, Celiac disease)
- Family history of renal stones, end stage kidney disease

PHYSICAL EXAMINATION

Should include a complete physical examination with special attention to the following:

- Vital signs: Heart rate, blood pressure (need to assess in relation to sex and height), respiratory rate, temperature, oxygen saturation
- Height, weight, head circumference (also BMI, growth velocity)
- Dysmorphic features, congenital abnormalities, systemic findings
- Some examples may include:
 - Aniridia (WAGR syndrome –Wilms tumour, aniridia, genitourinary anomalies, and intellectual disability)
 - Cataracts (Lowe’s syndrome, sequelae of steroid treatment)
 - Uveitis (in association with tubulointerstitial nephritis with uveitis)
 - Hemihypertrophy, branchial cleft fistulas or cysts, cleft palate, ear anomalies (Beckwith-Wiedemann syndrome, Branchio-oto-renal syndrome)
 - Cryptorchidism, absent abdominal wall musculature (Prune-Belly syndrome)
 - Spinal abnormalities (indicative of neurogenic bladder)
 - Polydactyly (Bardet-Biedl syndrome)
 - Imperforate anus
 - Ambiguous genitalia
- Examination for edema: periorbital, facial, sacral, scrotal/labial swelling, abdominal ascites, peripheral pitting edema

- CVS: pulses, blood pressure differential between upper and lower limbs, brachial-femoral delay, murmur, abdominal bruit, jugular venous pressure
- Resp: signs of fluid overload with crackles, tachypnea, work of breathing, stony dull percussion with pleural effusions
- Abdomen: abdominal distension, scars/ostomies/peritoneal dialysis catheter, ascites examination (fluid wave/shifting dullness), costovertebral angle tenderness, palpable kidneys (enlarged with ARPKD/ADPKD, obstructed kidneys, tumour)
- Bones: evidence of renal osteodystrophy i.e. rachitic rosary of chest, lower limb deformities (bowing of legs), widening of the wrists, frontal bossing
- Joint/skin examination to look for associated findings in autoimmune/vasculitic conditions or syndrome-related skin manifestations (e.g. angiofibroma, hypopigmented lesions, café au lait macules, stretch marks, buffalo hump, hyperpigmented areola/genitalia)

FURTHER READING

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2. DIAGNOSTIC TESTS

BLOODWORK

1. Creatinine: a product of muscle breakdown that is excreted by the kidneys. Used as a marker of kidney function. Should be interpreted with caution.
 - In neonates the serum creatinine is reflective of maternal serum creatinine for the first 72 hours of life after which it slowly falls to reflect neonatal values.
 - Creatinine is a less reliable marker in patients with low or above average muscle mass
2. Urea: a product of many biological pathways that is excreted by the kidneys. It is filtered in the glomerulus and a portion is reabsorbed in the kidney tubules.
 - Uremia can present with nonspecific signs and symptoms including altered mental status, nausea, vomiting, anorexia.
 - Other causes of high urea outside the kidneys include: high protein diet, GI bleed, steroids, in catabolic states. If high ratio compared with creatinine, suggestive of pre-renal state.
3. GFR: glomerular filtration rate
 - Gold standard way of measurement is by measuring inulin clearance (cumbersome test, not routinely done in clinical practice)
 - Other clearance markers used in place of inulin
 - (1) ^{51}Cr EDTA (ethylenediaminetetraacetic acid), DTPA (diethylenetriamine pentaacetate)
 - (2) 24-hour urine creatinine clearance also used as a surrogate marker for GFR
 - Estimated GFR (eGFR) calculated based on different formulas that use serum creatinine or cystatin C.
 - (1) A commonly used formula is the bedside Schwartz:

$$\text{eGFR} = 36.5 \times \text{height (in cm)} / \text{Cr } (\mu\text{mol/L})$$
4. Electrolytes: important indicator of kidney function. Electrolyte derangements may be indicative of worsening kidney function or specific disorders. Many abnormalities can be life-threatening and prompt and careful assessment is necessary! Don't forget to

measure extended electrolytes and save a urine sample for paired urine electrolytes where possible

- Basic electrolytes: Sodium, Potassium, Chloride, bicarbonate
- Extended electrolytes: Calcium*, Magnesium, Phosphate

*Total or ionized. If sending total, ensure albumin sent as well to correct for hypoalbuminemia.

5. Blood gas: Metabolic acidosis or alkalosis may be indicative of kidney pathology

- pH, bicarbonate

6. Albumin: Protein synthesized by the liver, responsible for acting as the transporter for many compounds and maintaining intravascular volume status.

- Hypoalbuminemia is a key feature of nephrotic syndrome, but it can also be low in protein losing enteropathy, inflammatory conditions, liver failure, sepsis, malnutrition
- High albumin in the context of high calcium, hemoglobin and hematocrit may hint at volume contraction

URINE TESTING

Urinalysis: A great deal of information can be obtained from the urinalysis.

- **pH**
 - Important in diagnosis of renal tubular acidosis
 - Alkaline urine may cause false positive protein on dipstick
- **Specific gravity**
 - May provide information about kidney concentrating ability
 - When interpreting the dipstick positive for protein or blood, low specific gravity may result in false negatives while high specific gravity can lead to false positive for protein/blood.
- **Blood**
 - Urine dip measures hemoglobin, not red blood cells
 - Free myoglobin in the urine can create false positive

- Microscopic hematuria is defined as >5 RBC per high powered field (as seen on urine microscopy)
- **Protein**
 - A urine sample is positive for protein if the dipstick is $\geq 1+$ in a urine sample with a specific gravity of ≤ 1.015
 - Proteinuria is an important marker of kidney disease
 - Urine dipstick measures predominantly albumin but other forms of protein can also be lost in the urine
 - (i.e. Exclusively tubular proteinuria – typically low molecular weight proteins - may not result in a positive urine dip for protein)
 - Degree of proteinuria is important in diagnosis (ie. $\geq 3+$ is nephrotic range – look for other features of nephrotic syndrome)
- **Leukocytes**
 - Pyuria is defined as ≥ 3 WBC per high power field
 - Can be positive in a cystitis or pyelonephritis, but it is important to check how the sample was taken (catheter sample or suprapubic aspirate would be the most reliable method of sampling to assess for infection)
 - Sterile pyuria is seen in certain viral or fungal infections, and Kawasaki disease
- **Nitrites**
 - Positive in the presence of specific bacteria that convert nitrate to nitrite
 - Some organisms that do not do this are Enterococcus, Pseudomonas and Acinetobacter
 - Often falsely negative in infants as urine is not held long enough in bladder for nitrites to form

Urine culture

- Bacterial growth indicates urinary tract infection, minimum colony counts depend on method of urine collection
 - Clean catch: $\geq 10^5$ CFU/mL
 - In-and-out: $\geq 5 \times 10^4$ CFU/mL
 - Suprapubic aspiration: $\geq$ Any growth

Urine protein: better quantification of urine protein can be obtained by the following

- 24-hour urine protein – most accurate way to quantify proteinuria
 - Entire urine volume over 24 hours is collected and measured
 - Difficult to obtain in infants and young children
 - Normal $< 100 \text{ mg/m}^2/\text{day}$ (or $< 150 \text{ mg/day}$)
 - Nephrotic Range $> 1000 \text{ mg/m}^2/\text{day}$ (or $> 3.5 \text{ g/day}$)
- Spot Urine protein-to-creatinine ratio (PCR) – a substitute measurement that is easier to obtain and highly correlates with 24-hour urine protein
 - Units: mg or g of protein/mmol of creatinine. Ensure units are correct when calculating!
 - Normal:
 - Less than 2 years of age: $< 50 \text{ mg/mmol}$
 - Greater than 2 years of age: $< 20 \text{ mg/mmol}$ ($< 0.02 \text{ g/mmol}$ in some centres)
 - Nephrotic range:
 - Greater than 250 mg/mmol creatinine ($> 0.2 \text{ g/mmol}$ in some centres)
- Spot Urine albumin-to-creatinine ratio (ACR) can be used as well. It can help to distinguish glomerular proteinuria (ACR) from glomerular + tubular proteinuria (PCR). Used in diabetic nephropathy.
 - Units: mg of albumin/mmol of creatinine
 - Normal $< 2.5 \text{ mg/mmol}$
 - $2\text{-}20 \text{ mg/mmol}$ creatinine mildly increased
 - $20\text{-}220 \text{ mg/mmol}$ creatinine moderately increased
 - Nephrotic range $> 220 \text{ mg/mmol}$ creatinine

Urine electrolytes:

- Used to investigate many serum electrolyte disturbances, assess for kidney tubular disorders, fluid status (hypovolemia), monitor progression of kidney function
- 24 hr Urine sodium can sometimes help estimate sodium intake

- Fractional Excretion of Sodium (FENa) %

$$= 100 \times \left[\frac{\text{Urine sodium (mmol/L)} \times \text{Serum creatinine (mmol/L)}}{\text{Serum sodium (mmol/L)} \times \text{Urine creatinine (mmol/L)}} \right]$$

- <1% suggests pre-renal etiologies, >2% suggests intrinsic renal
- *Please see Acute Kidney Injury chapter for further details on how to calculate and interpret the fractional excretion of sodium (FENa)

- Other useful formulas:

- Transtubular potassium gradient (TTKG) to assess potassium excretion in the urine (described further in electrolytes chapter)

$$\text{TTKG} = \text{Urine}_K / \text{Blood}_K \times \text{Blood}_{\text{osm}} / \text{Urine}_{\text{osm}}$$

- Should be low in hypokalemia, high in hyperkalemia

- Tubular reabsorption of phosphate (TRP) to assess phosphate reabsorption

$$1 - \left[\frac{\text{Urine phosphate} \times \text{Serum creatinine}}{\text{Serum phosphate} \times \text{Urine creatinine}} \right] \times 100$$

- Normal should be >82%

Urine microscopy: Visualization of urine under microscope, may provide additional clues to underlying kidney disease

- RBC casts
 - Pathologic, suggests glomerular injury (ie. Glomerulonephritis)
- WBC casts
 - Typically seen in tubulointerstitial disease such as acute pyelonephritis or allergic interstitial nephritis
- Hyaline casts
 - A few (1-2) per high powered field are normal
 - Increased number can be seen in the context of strenuous exercise or dehydration
- Granular casts
 - Suggests stasis within the nephron
 - Can be associated with tubular necrosis

Urine stone studies: done when there are concerns for nephrolithiasis

- Urine calcium, oxalate, citrate, uric acid, all normalized for urine creatinine or urine osmolality
- Urine amino acids can be used to look for cystine (in some centres a urine nitroprusside may be done as a screening test for cystinuria)
- See Urolithiasis chapter for more details

DIAGNOSTIC IMAGING

Kidney ultrasound can visualize the following:

- Location and size of kidneys
- There are normal graphs for kidney size based on age and child's height. Kidneys are normally located in the flanks, but can be ectopic (e.g. in the pelvis)
- Structural abnormalities
 - Ex. Hydronephrosis, cysts, horseshoe kidney, duplex collecting systems
- Hyperechoic or hypoechoic areas – may be seen in acute pyelonephritis
- Well defined hypoechoic or anechoic mass and absence of internal flow on power doppler (may also include loculations or septations) – kidney abscess
- Increased kidney echogenicity – a nonspecific finding that may be indicative of parenchymal disease
- Dense calcifications, bright echogenic foci with posterior acoustic shadowing, twinkle artefacts – findings of nephrolithiasis
- Irregular, focal indentations in the cortex overlying the medullary pyramids – suggest areas of scarring
- Doppler ultrasound - used to assess arterial and venous flow of the kidney, useful if clinical concern for thrombosis
 - Useful to see flow through renal arteries, assess for renal artery stenosis, renal vein thrombus, arteriovenous malformations

CT Scan

- Can be helpful to see stones that aren't seen on US

- CT angiogram is better than US at detecting renal artery stenosis
- Watch out for contrast with CT, may cause kidney injury!

DMSA (dimercapto succinic acid)

- Static scan that shows uptake of tracer to the kidneys. Gold standard to detect pyelonephritis. Useful for detecting kidney parenchymal defects/scarring and to assess differential function.
- Normal findings are equal uptake to both kidneys (approximately 50% each)
- Areas of scarring may be indicated by reduced uptake of the tracer

MAG-3 (mercaptoacetyltriglycine)/DTPA

- Dynamic scans that can give you a nuclear medicine GFR
- MAG-3 is a tracer better suited to assess renal tubular function and is used to look for urinary tract obstruction (e.g. UPJ obstruction)
- DTPA is better suited to assess glomerular function (used for GFR determination)

VCUG

- Gold standard to diagnose vesico-ureteral reflux (VUR) and posterior urethral valves (PUV)
- Fluoroscopic study to assess the lower urinary tract (urethra, bladder, ureters)
- Dye inserted through urethra (via catheter) and images taken to watch flow
- Should not be done during an acute infection as it may falsely overestimate the VUR and increase risk of sepsis
- In girls, can consider using a nuclear cystogram: less radiation, detects reflux, but doesn't provide as detailed anatomy (can't visualize urethra)

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3. KIDNEY DEVELOPMENT

INTRODUCTION

The kidney is a critical organ for eliminating metabolic waste products and maintaining key homeostasis of pH, ion concentrations, and hormone status, as mentioned in the introduction.

Nephrons and the collecting duct system perform the daily functioning of the kidney.

HUMAN KIDNEY DEVELOPMENT

- Human kidney development begins in the 5th week of gestation, with the first functioning nephrons making urine by the 9th week.
- New nephrons continue to form until approximately 32–34 weeks gestation.
- Further renal growth results from the growth and maturation of already formed nephrons rather than new nephrons.
- In fetal or perinatal renal injury, the developing kidney is incapable of compensating for irreversible nephron loss.
- The number of nephrons formed at birth is an essential determinant of renal function later in life.
- Nephron endowment at birth is a crucial fetal factor that may have long term impact on the development of hypertension and chronic kidney disease (CKD) in adults.

ANATOMY OF THE KIDNEY

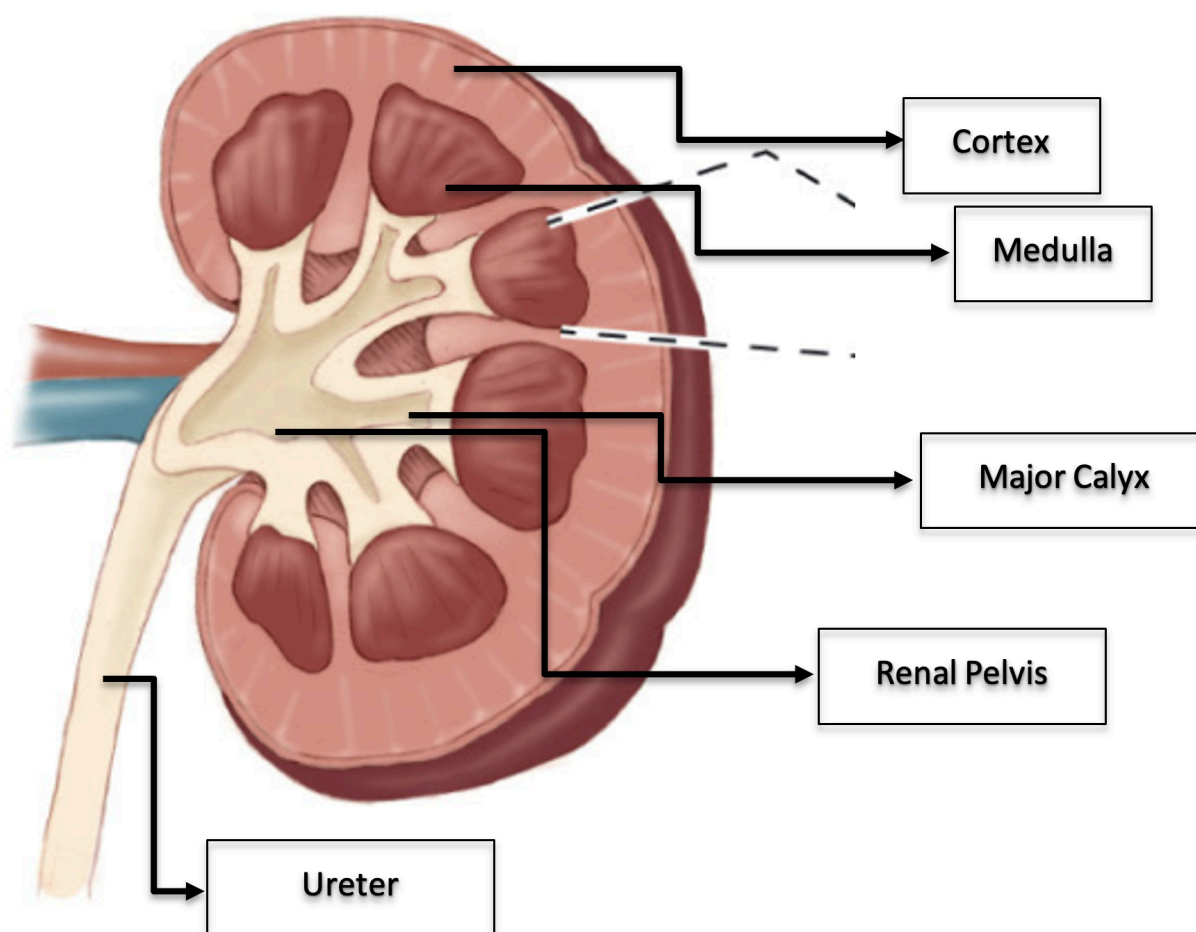
The renal anatomy can be described in two basic forms for teaching purposes:

Gross anatomy

- The average renal length by ultrasound in healthy newborns is (4.21 +/- 0.45) cm for the right kidney and (4.32 +/- 0.46) cm for the left kidney. They grow with age at about 0.5 cm to 1 cm per year and achieve adult length by approximately by 18 years of age.

- Both kidneys are located retroperitoneally, at the posterior aspect of the abdominal wall, with the right one slightly lower than the left.
- Each kidney has two layers with an outer layer called the cortex and inner brighter red called the medulla

Kidney



- Each kidney has a collection of triangular renal pyramids, or lobes, with a base bordering the cortex and an apex projecting as renal papillae into the minor calyces.
- Each renal pyramid consists of medullary tissue associated with the corresponding cap of cortical tissue.
- Minor calyces join to form the major calyces, which ultimately unite to form the ureter.
- The ureter is 25 cm long in an adult but has a variable length in children.
- The ureter enters the urinary bladder posteriorly on each side.
- The urinary bladder is a hollow muscular organ located posterior to the symphysis pubis, and a reflection of the peritoneal lining covers its superior surface.

Figure 3.1. Gross Kidney Anatomy.

Figure used with permission from: Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *The Lancet*. 2018 Jul 7;392(10141):61-74.

Microscopic anatomy

- The renal parenchyma consists of functional units called uriniferous tubules, which consist of two components:
 - **The nephrons:** the “functional units” of the kidney; cleanse the blood and balance the constituents of the circulation.

- The nephron consists of the Bowman capsule (the most proximal structure of nephron), proximal convoluted tubules (PCTs), the loop of Henle, and distal convoluted tubules (DCTs).
- Nephrons have highly variable lengths, with the superficial (cortical) nephrons are shorter, and the deep (juxtamedullary) nephrons are longer, mainly depending on the length of the loop of Henle.
- Nephrons with glomeruli close to the corticomedullary junction have long loops of Henle, which participate in the urinary concentration mechanism
- **The collecting tubules:**
 - The last component of the nephron have squamous epithelium, whereas the collecting ducts have taller epithelial cells, starting as cuboidal cells in the cortex but growing taller along the route of descent to the renal papilla

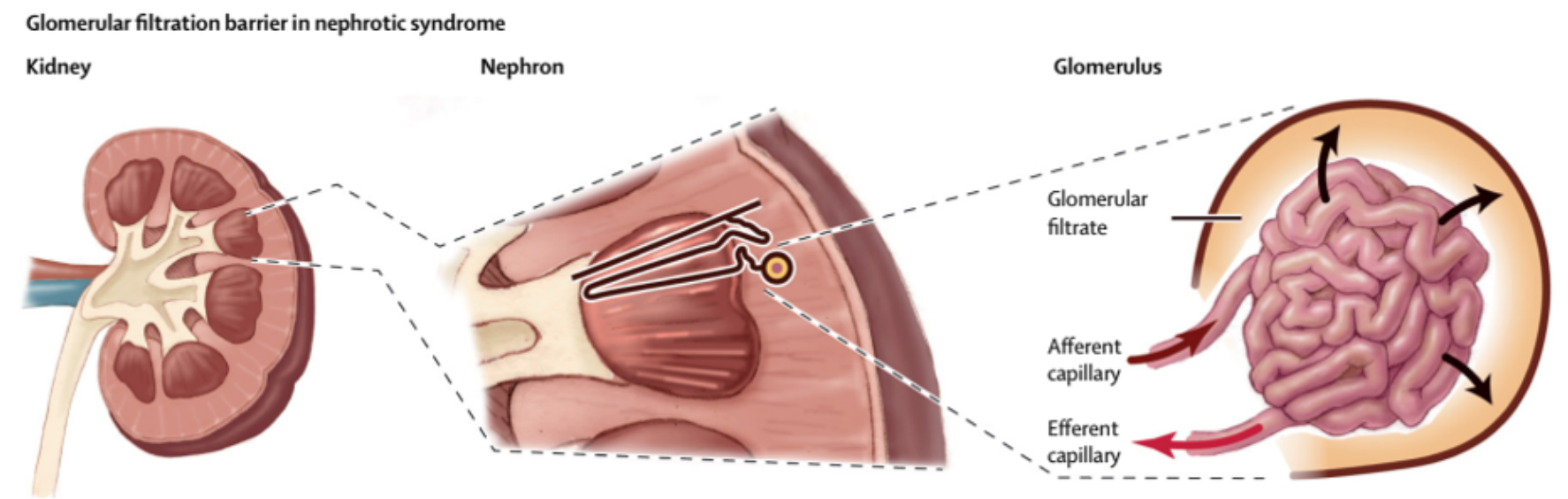


Figure 3.2.

Figure used with permission from: Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *The Lancet*. 2018 Jul 7;392(10141):61-74.

Blood supply of the kidney

- Blood flow through the kidneys is surprisingly extensive (approximately 25% of cardiac output), ensuring rapid removal of wastes from the blood.
 - 90% flows through the cortex and the rest flowing through the medulla.
- The **renal artery** enters the renal sinus and divides into anterior and posterior branches, forming **segmental arteries**.
- **Segmental arteries** → **lobar arteries** for each renal pyramid (lobe) → branch further into **interlobar arteries** between the renal pyramids

- Once the interlobar arteries have penetrated to the corticomedullary junction, → branch into arcuate arteries, which run parallel to the surface of the kidney.
- At regular intervals along the arcuate arteries, interlobular arteries project radially toward the most superficial parts of the cortex.
- As the interlobular arteries pass from the deep cortex to the superficial cortex, they send out branches called afferent arterioles that supply blood to the glomeruli. After leaving the glomerulus, blood enters the efferent arteriole.
- These blood vessels drain into interlobular veins, arcuate veins, interlobar veins, and eventually the renal vein.

Important medications to note that act on the afferent and efferent arteriole:

- NSAIDs and calcineurin inhibitors vasoconstrict afferent arteriole & decrease GFR
- Prostaglandins vasodilate afferent arteriole and increase GFR
- Angiotensin II preferentially vasoconstricts efferent, driving up intraglomerular pressure and increases GFR
- Therefore, Angiotensin converting enzyme (ACE) inhibitors do the opposite, vasodilating the efferent to lower intraglomerular pressure and decrease GFR

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4. FLUIDS AND ELECTROLYTES

MAINTENANCE FLUIDS

First rule in nephrology to remember: the 4-2-1 rule is not always the right answer for maintenance fluids! Maintenance fluid requirements based on the 4-2-1 rule which are used in other areas of paediatrics were calculated based on healthy children and their calorimetric losses, which don't always apply to children in hospital. If children have experienced an AKI, have polyuria or oliguria, or if they have an electrolyte abnormality, "maintenance" fluids per the 4-2-1 rule may not be an appropriate treatment.

Therefore, maintenance fluid requirements = insensible losses (skin losses, respiratory system losses, typical GI water losses) + urine output.

In admitted patients, we may need to consider additional losses in the form of vomiting, diarrhea, CSF drain, abdominal or chest drains.

Insensible losses in children/day = approximately 400 mL/m² of Body Surface Area

Formula for Body Surface Area:
$$BSA(m^2) = \sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}}$$

HYPONATREMIA

You may have heard that sodium problems are actually water problems...it's true! Hyponatremia is a disorder of water balance – mediated by either appropriate or inappropriate ADH production.

Step by step:

1. Identify hyponatremia (Na⁺ <135 mmol/L).
2. Check serum osmolality:
 - Low = true hyponatremia

- Normal = hyperproteinemia/hyperlipidemia
- High = glucose/mannitol (pseudohyponatremia).

3. Next, assess volume status to identify the cause:

- Hypovolemia (Total body water ↓, Total body Na+ ↓ ↓)
 - Check urine Na+
 - Urine Na+ >20 mmol/L: renal losses (i.e. diuretics, mineralocorticoid deficiency, salt wasting, osmotic diuresis)
 - Urine Na+ <20 mmol/L: extrarenal losses (i.e. vomiting, diarrhea, third spacing, pancreatitis)
- Euvolemia (Total body water ↑, Total body Na+ the same)
 - Urine Na+ generally >20 mmol/L
 - Syndrome of inappropriate anti-diuretic hormone excretion (SIADH), stress, hypothyroidism, glucocorticoid deficiency, certain medications
 - Variable etiologies of SIADH: CNS disorders (infection, stroke, hemorrhage, trauma), medications, respiratory infections, malignancies, pain, nausea.
 - Examples of medications that can cause SIADH: anti-epileptic medications such as carbamazepine and valproate, chemotherapy such as vincristine, and cisplatin, antipsychotic medications such as haloperidol and amitriptyline, NSAIDs, exogenous DDAVP.
 - SIADH biochemical features include hyponatremia, evidence of inappropriate urinary concentration (UOsm > 100 mOsm/kg), low plasma osmolality (<270 mOsm/kg)
- Hypervolemia (Total body water ↑ ↑, Total body Na+ ↑)
 - Check urine Na+
 - Urine Na+ >20 mmol/L: Consider AKI/CKD
 - Urine Na+ <20 mmol/L: Consider Nephrotic syndrome, cirrhosis, heart failure

4. When assessing hyponatremia, it is important to note the following: fluid balance for the preceding days (total intake, total output and balance), daily weights, serum sodium, the sodium content of any fluid/diet intake they have, and urinary sodium to help guide us to the etiology and management.

5. Treatment – varies according to etiology:

- Acute hyponatremia
 - Are there severe symptoms, such as seizures, loss of consciousness, coma, lethargy?
 - If yes, then give 3% saline (2-3 mL/kg over 20 min)
 - 3% saline = 513 mmol/L of Na⁺
 - Repeat x 2 until symptoms resolve or there has been a 5 mmol/L rise in Na⁺
- Hypovolemic hyponatremia
 - ABC's come first! Give NS bolus if required from a circulation standpoint and a volume perspective, and then deal with the sodium correction. Be sure to account for the sodium given in your bolus as part of your sodium deficit.
 - Avoid rapid correction because in chronic hyponatremia if you correct too rapidly, can get osmotic demyelination.
 - Once symptom free, we want to raise Na⁺ by no more than 8-10 mmol/L in first 24 hrs
 - **Please note: There are multiple formulas that can be used to correct sodium for hypovolemic hyponatremia. One option is provided below. Remember that no formula is perfect all the time – there are many variables that we cannot account for. Always check labs frequently to ensure you are moving in the right direction, at the right pace, and change your plan if needed.**
 - Correcting hypovolemic hyponatremia using the Sodium deficit formula
 - Replace the sodium deficit (i.e. the amount of Na missing), and provide a 'maintenance' amount of continuing sodium to account for ongoing losses (~2 mmol/kg/day).
 - Sodium deficit = **0.6 x weight (i.e. TBW) x (Desired – current sodium)**
 - Then, once deficit is determined, use cross multiplication to determine the volume of normal saline required to correct
 - The sodium content of various fluids can be found below.

D5W	0 mmol/L Na ⁺
0.2NS	34 mmol/L Na ⁺
0.45NS	77 mmol//L Na ⁺
0.9NS	154 mmol/L Na ⁺

EXAMPLE: Let's say someone has a serum Na of 112. You want it to raise to no more than 120 in the next 24 hours.

$$\text{Sodium deficit} = 0.6 \times 10 \text{ kg} \times (120 - 112) = 48 \text{ mmol}$$

$$\text{Using 0.9 NS: } 1000 \text{ mL} / 154 \text{ mmol} = x \text{ mL} / 48 \text{ mmol}$$

$$x = 311 \text{ mL} / 24 \text{ hours} = 13 \text{ mL/hr of NS}$$

- Giving 13 mL/hr of 0.9 NS will replace the sodium deficit over 24 hours
- However, we must also account for ongoing sodium losses. You can do this by:
 - Estimating a 'maintenance' sodium of 2 mmol/kg/day
 - $2 \text{ mmol} \times 10 \text{ kg} = 20 \text{ mmol/day}$ of maintenance sodium.
 - Using 0.9 NS: $1000 \text{ mL} / 154 \text{ mmol} = x \text{ mL} / 20 \text{ mmol}$, $x = 130 \text{ mL} / 24 \text{ hours} = 5 \text{ mL/hr}$
 - Final script: $13 \text{ mL/hr} + 5 \text{ mL/hr}$ (deficit + maintenance sodium) = 18 mL/hr of IV NS
 - Another way to account for 'maintenance' sodium is to measure their urine sodium and replace the urine output regularly mL:mL with a solution that matches the urine sodium.
- Keep NPO, measure labs in 2-4h, measure and monitor urine output, measure urine sodium q 4-6 hrs if possible
- **Watch out!** If you see the urine output increasing suddenly – this may indicate that Na is rising rapidly because of excess volume replacement and ADH getting suppressed too quickly. This may lead to more urinary free water clearance.
- Euvolemic Hyponatremia (e.g. SIADH)
 - Fluid restrict, stop drugs that could cause SIADH and stop hypotonic fluids
 - Restrict fluids to $2 \times \text{insensible losses} = 2 \times 400 \text{ mL/m}^2/\text{day} = \text{max } 1 \text{ L}$
 - Can also give furosemide to help with free water clearance
 - Vasopressin receptor antagonists not routinely used in pediatrics. Urea supplementation can be considered if chronic.
- Hypervolemic hyponatremia

- Increased ADH and aldosterone with salt and water retention, but effective circulating volume may still be depressed
- Therefore need to fluid restrict, increase free water excretion
- If hypoalbuminemic (e.g. with nephrotic syndrome or liver failure), consider giving 25% Albumin (0.5-1 g/kg) over 4 hours + Furosemide (1 mg/kg) midway and at the end of the infusion to mobilize fluid and improve low extracellular volume

HYPERNATREMIA

Hypernatremia is also a disorder of water balance, usually related to a deficit of free water (most commonly hypernatremic dehydration). Again, we want to avoid rapid correction because the brain generates its own osmoles to compensate for the hypertonicity and cells shrinking. If you correct too rapidly, can get cerebral edema. Sodium should drop by no more than 8-10/24 hrs, to prevent cerebral edema.

Step by step:

1. Identify hypernatremia ($\text{Na}^+ > 145 \text{ mmol/L}$).
2. Causes of hypernatremia: free water deficit due to water loss, or decreased water intake/salt gain.
 - If urine osmolality $<$ serum osmolality: Consider Diabetes insipidus (central/nephrogenic)
 - If urine osmolality $>$ serum osmolality: Consider renal losses, GI losses, skin, lungs, decreased access to free water, decreased thirst
 - Sodium gain due to salt poisoning (very rare)
 - Sodium gain due to iatrogenic causes
3. Restore intravascular volume – ABC's! Bolus with 20 – 60 mL/kg of NS.
4. Calculate free water deficit (FWD) = $0.6 \times \text{weight} [(\text{Na}_{\text{actual}} - \text{Na}_{\text{desired}})/\text{Na}_{\text{desired}}]$
 - **EXAMPLE:** Weight 9 kg, serum Na^+ 174 mmol/L
 - Free Water Deficit = $0.6 \times 9 \text{ kg} [(174 \text{ mmol/L} - 145 \text{ mmol/L})/145 \text{ mmol/L}] = 1080 \text{ mL}$ of free water
 - Another strategy:
 - A general correction of 4 mL/kg of free water should lower sodium by 1 mmol/L
 - Ex: $174 - 145 = 29$.
 - $4 \text{ mL/kg} \times 9 \text{ kg} \times 29 = 1044 \text{ mL}$ free water (very similar to free water deficit calculation above)
5. This is the total free water deficit, but we want to correct slowly (no more than 8-10 mmol/24 hours), so this 1080 mL should be given over 3.5 - 4 days = 270 mL of free water/24 hours
6. Choose the correct fluid to use to replace the free water deficit.

- How much Na⁺ is there in each solution?

D5W	0 mmol/L Na ⁺
0.2NS	34 mmol/L Na ⁺
0.45NS	77 mmol/L Na ⁺
0.9NS	154 mmol/L Na ⁺

- How much free water in each solution?
 - The amount of free water depends on the amount of sodium in the solution as well as the patient's serum sodium.
- % Free water in any solution = $1 - (\text{Solution}_{\text{Na}} / \text{*Serum}_{\text{Na}}) \times 100\%$
- *Use your patient's serum sodium to determine the amount of free water for your patient

D5W	$1 - (0/174) \times 100\% = 100\%$
0.2NS	$1 - (34/174) \times 100\% = 80\%$
0.45NS	$1 - (77/174) \times 100\% = 56\%$
0.9NS	$1 - (154/174) \times 100\% = 11\%$

- Using the above table, you can see for example, that every 1L of 0.2NS would provide about 800 mL of free water in this case.
- So now we need to figure out how much of each solution you would need in order to provide 270 mL of free water (that we calculated above)

D5W	270 mL of free water
0.2NS	$270/800 \text{ mL (i.e. 80\% of 1L)} \times 1000 \text{ mL} = 337 \text{ mL}$
0.45NS: most often choose this	$270/560 \text{ mL (i.e. 56\% of 1L)} \times 1000 \text{ mL} = 482 \text{ mL}$
0.9NS	$270/110 \text{ mL (i.e. 11\% of 1L)} \times 1000 \text{ mL} = 2450 \text{ mL}$

- Calculate the insensible losses = 400 mL/m²/day. BSA is approximately 0.4 m² in this case. Therefore, insensible losses = 160 mL/day.
- Add together insensibles + deficit = 160 mL/24 hours + 482 mL of 0.45 NS/24 hours = 27 mL/hr of 0.45 NS. Add dextrose to this fluid to provide glucose.
- Next, need to account for ongoing future losses (urine/GI). Replace this 1:1 q 2-4 hours depending on amount of losses. Try to match the sodium content of the replacement

fluid to the sodium content of the losses (i.e. if urine sodium is 70 mmol/L, replace with 0.45 NS = 77 mmol/L of Na⁺).

Type of Fluid	Na	K	Cl
<i>Gastric</i>	50	10-15	150
<i>Ileostomy</i>	130	15-20	120
<i>Diarrhea</i>	50	35	40
<i>Sweat</i>	50	5	55
<i>Blood</i>	140	4-5	100
<i>Urine</i>	0-100	20-100	70-100

10. Final prescription = Insensibles + Deficit + Ongoing losses = 27 mL/hr of D5/0.45NS with mL:mL urine output replacement with 0.45 NS every 2 hours. To be safe, you can start replacing urine output with NS instead of 0.45 NS until you can obtain a urine sodium to confirm the correct solution to replace the urine with, to not drop the sodium too quickly.
11. If able to use the enteral route (no contraindications), can be more physiologic to replace free water deficit through po/NG route.
12. Make sure you keep checking serum and urine electrolytes frequently, monitor ins and outs, and adjust prescription as necessary.

HYPERKALEMIA

Although hyperkalemia is one of our few true renal emergencies, it can be approached and treated in a systematic fashion.

Step by step:

1. Identify hyperkalemia ($K^+ > 5.5$ mmol/L).
2. ***Confirm sample** (i.e. repeat if concerned about hemolysis, thrombocytosis, etc.)
3. Obtain ECG and place on cardiac monitor.
 - Look for arrhythmia, prolonged PR interval, peaked T waves, absent P wave, widening QRS, ST depression.
4. Emergency management:
 - Stop any sources of potassium
 - Calcium gluconate (50-100 mg/kg, max 2000 mg) x 1 to stabilize cardiac membrane
 - To shift the potassium intracellularly:
 - Salbutamol (Ventolin) nebulizer (usually the quickest available) <10 kg: 2.5 mg; >10 kg: 5 mg: repeat back to back x 3
 - Sodium bicarbonate (1 mEq/kg IV – max 50 mEq) x 1 (if acidotic)
 - Dextrose and Insulin: Dextrose 0.5 g/kg/dose IV over 2-5 min + Insulin (Humulin R) 0.1 units/kg, max 10 units IV push.
 - If non-diabetic, can trial giving just dextrose bolus and patients' own insulin surge should also help to shift potassium
 - To eliminate potassium:
 - Sodium Polystyrene (Kayexalate®) (1g/kg/dose PO, max 15 g) to help excrete potassium in the stool if no contraindication from GI standpoint/not in the NICU
 - Furosemide (1 mg/kg IV).
 - Dialysis if all else fails.
5. Assess etiology
 - Abnormal GFR – AKI, CKD, excess potassium intake, GI bleed, hemolysis, transfusion, rhabdomyolysis, drugs impairing potassium excretion
 - Normal GFR – low aldosterone, aldosterone insensitivity, medications

- Transtubular potassium gradient: $TTKG = \frac{Urine_K}{Blood_K} \times \frac{Blood_{osm}}{Urine_{osm}}$
 - Can be used as a surrogate marker of aldosterone activity
 - $TTKG < 6$ = impaired aldosterone bioactivity, $TTKG > 6$ = renal response is intact
 - There are questions regarding the validity of this formula due to urea recycling in the medullary collecting duct, though it is still used. Conditions of use include urine sodium needs to be > 20 mmol/L, and urine osmolality must be greater than serum osmolality.
 - Instead, could consider using urine K/Creatinine ratio (in hypokalemia should be < 1.5 , in hyperkalemia it should be > 20)
- Low renin/low aldosterone: interstitial nephritis, obstructive uropathy
- Normal/high renin/low aldosterone: primary hypoaldosteronism, congenital adrenal hyperplasia, medications
- High Aldosterone (aldosterone resistance/insensitivity): obstructive uropathy, drugs, post-transplant, pseudohypoaldosteronism type 1 or 2

HYPOKALEMIA

Potassium lives primarily intracellularly (concentration = 150 mmol/L intracellularly, 3.5-5 mmol/L extracellularly)

Symptoms: muscle weakness, paralysis, cardiac arrhythmias

Step by step:

1. Identify Hypokalemia, $K < 3.5$. Assess for symptoms.
2. Obtain ECG to look for U waves, ST depression
3. Treat by giving potassium replacement IV (if unable to take oral or symptomatic) or Oral potassium replacement
 - If IV, need ECG monitoring, may need central line if giving larger concentration
 - If acidotic – suggest K citrate
 - If alkalotic – suggest K chloride
 - If proximal RTA – may need K phosphate
 - Can consider using potassium sparing diuretics if not hypovolemic
4. Assess etiology
 - Depletion (decreased intake due to malnutrition or malabsorption)
 - Increased losses (Renal – urine $K > 20$ mmol/L – due to elevated mineralocorticoid activity – will see hypertension, or excess tubular losses – i.e. diuretics, Bartter's, Gitelman's)
 - Transcellular shift – alkalosis, hypothermia, beta agonist, insulin
 - ***Special note:** Low magnesium releases magnesium inhibition of ROMK channels, which increases potassium secretion. Therefore, always make sure to correct hypomagnesemia as well when treating hypokalemia

ACID-BASE DISORDERS

This is a general approach you can use for interpreting acid-base problems. Since this is nephrology, we will focus primarily on metabolic acidosis and metabolic alkalosis.

Overview:

- $\text{pH} = -\log [\text{hydrogen in nmol/L}]$
- <7.35 acidemia, >7.45 alkalemia
- Free hydrogen is active – destructive, binds to proteins, affects cellular structure and function
- *Special Note: Hydrogen cations can displace calcium bound to albumin and increase free calcium level.
 - If pH low (acidosis), ionized calcium high, if pH high (alka-LOW-sis), ionized calcium low.
 - When both acidemia and hypocalcemia, must correct calcium first before acidemia. If you correct acidosis first, ionized calcium will drop.
- Main hydrogen buffers are bicarbonate, hemoglobin, phosphate and bone

Step by Step:

1. Look at the pH. If <7.35 – acidosis. If >7.45 – alkalosis.
2. If pH <7.35 , look at the bicarb (HCO_3). If low – metabolic acidosis. If not, look at the pCO_2 – if high – respiratory acidosis.
3. If pH >7.45 , look at the bicarb. If high – metabolic alkalosis. If not, look at the pCO_2 – if low – respiratory alkalosis.
4. Next step is to look at compensation. Remember that compensation always corrects the pH TOWARDS normal – it doesn't overcorrect.
 - Respiratory compensation happens quickly. Metabolic compensation takes days.
 - Metabolic acidosis – pCO_2 must drop to compensate:
 - Expected $\text{pCO}_2 = (1.5 \times \text{HCO}_3) + 8 \pm 2$
 - Metabolic alkalosis – pCO_2 must increase to compensate:
 - Expected $\text{pCO}_2 = 0.7 \times \text{HCO}_3 + 20 \pm 1.5$

- Generally expected compensation
 - Acute respiratory acidosis – $\uparrow \text{HCO}_3^-$: $\uparrow \text{pCO}_2 = 1:10$
 - Acute respiratory alkalosis – $\downarrow \text{HCO}_3^-$: $\downarrow \text{pCO}_2 = 2:10$
 - Chronic respiratory acidosis – $\uparrow \text{HCO}_3^-$: $\uparrow \text{pCO}_2 = 3:10$
 - Chronic respiratory alkalosis – $\downarrow \text{HCO}_3^-$: $\downarrow \text{pCO}_2 = 4:10$
- Alternative method of approaching compensation:

Acid-Base Issue	Normal Compensation
Metabolic acidosis	For every $\downarrow 1 \text{ mmol HCO}_3^-$, $\text{pCO}_2 \downarrow$ by 1.2 (increase RR)
Metabolic alkalosis	For every $\uparrow 1 \text{ mmol HCO}_3^-$, $\text{pCO}_2 \uparrow$ by 0.6 (decrease RR)
Respiratory acidosis (acute)	For every $\uparrow 1 \text{ mm pCO}_2$, $\text{HCO}_3^- \uparrow$ by 0.1 mmol/L (renal excretion)
Respiratory acidosis (chronic, 3-5 days)	For every $\uparrow 1 \text{ mm pCO}_2$, $\text{HCO}_3^- \uparrow$ by 0.4 mmol/L (renal excretion)
Respiratory alkalosis (acute)	For every $\downarrow 1 \text{ mm pCO}_2$, $\text{HCO}_3^- \downarrow$ by 0.1 mmol/L (renal excretion)
Respiratory alkalosis (chronic, 3-5 days)	For every $\downarrow 1 \text{ mm pCO}_2$, $\text{HCO}_3^- \downarrow$ by 0.4 mmol/L (renal excretion)

- If the compensation is as expected, then great! Only one acid-base disorder we need to figure out. However, if it is not, then there is a mixed picture.
- For example, in metabolic acidosis, if the pCO_2 is lower than expected for compensation, then there is concurrent respiratory alkalosis. If it is higher than expected for compensation, then there is concurrent respiratory acidosis.

5. Next step, assess the etiology.

- Metabolic Acidosis
 - Either through loss of bicarbonate (in which chloride must increase to maintain electroneutrality) OR addition of acid (as an anion, so chloride does not need to change)
 - Calculate the anion gap: $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$. Normal anion gap is between 8-12.
 - Elevated anion gap – think MUDPILES
 - Methanol, Uremia, DKA, Paraldehyde/propylene glycol, Iron/inborn errors of metabolism, Lactate, Ethanol/ethylene glycol, Salicylates
 - Normal anion gap – think renal or GI loss of bicarbonate. Usually lost with cation (Na) – anion gap is unchanged.

- GI losses – diarrhea, fistula, stoma losses
- Renal – look at Urine pH and urine anion gap
- Urine anion gap = $\text{Na}^+ + \text{K}^+ - \text{Cl}^-$. This represents the unmeasured anion in urine (ammonium, NH_4^+) which is how the kidney secretes acid.
- If urine anion gap positive, this represents LOW ammonium, could be representative of RTA
- If urine anion gap negative, this represents HIGH ammonium, appropriate kidney compensation, and usually GI losses of bicarb.
- For further details on Renal Tubular Acidosis, please see tubulopathies chapter.
- Urine pH >5.5 – think about distal RTA
- Urine pH <5.5 + Low K – think about proximal RTA
- Urine pH <5.5 + High K – think about hyperkalemic RTA (Type IV), i.e. low aldosterone, aldosterone insensitivity, renal failure or obstructive uropathy
- Metabolic alkalosis
 - Secondary to Low H^+ or High Bicarb
 - Causes of low H^+
 - Transcellular shift. Exchange of hydrogen for potassium. If hypokalemia, K^+ comes out of the cell to replace, H^+ goes into the cell
 - H^+ loss through kidney (mineralocorticoid action, or linked to more distal sodium delivery with diuretics/tubulopathies).
 - We reabsorb sodium in exchange for potassium/hydrogen to maintain balance $\Rightarrow$ more sodium reabsorption $\Rightarrow$ more K^+ and H^+ secretion
 - H^+ loss through GI tract (vomiting)
 - Causes of high bicarb
 - Excess alkali administration (iatrogenic)
 - Chronic respiratory acidosis – if suddenly resp acidosis is corrected, left with metabolic alkalosis that takes days to reverse
- Combination
 - “Contraction” or Chloride-depletion alkalosis

- Dehydration leads to decreased GFR which leads to decreased bicarb excretion
- Dehydration leads to Renin-angiotensin-aldosterone system activation
- Chloride depletion blocks distal bicarb secretion through chloride/bicarbonate exchanger
- Milk Alkali syndrome – excess calcium carbonate: triad of hypercalcemia, pre-renal AKI, metabolic alkalosis (due to both dehydration AND excess alkali with the “carbonate”)

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2

SECTION 2

Acute Problems in Paediatric Nephrology

OUTLINE

5. Acute Kidney Injury
6. Approach to Proteinuria
7. Hypertension in Children
8. Approach to Hematuria

Abbreviations

ANCA = antineutrophil cytoplasmic antibodies

AKI = Acute kidney injury

ARF = acute renal failure

ATN = Acute tubular necrosis

BUN = blood urea nitrogen

CNI = calcineurin inhibitors

C3G = C3 glomerulopathy

eCCl = estimated creatinine clearance

eGPA = eosinophilic granulomatosis with polyangiitis

FENa = fraction excretion of sodium

FSGS = focal segmental glomerulosclerosis

GBM = glomerular basement membrane

GN = glomerulonephritis

GFR = glomerular filtration rate

GPA = granulomatosis with polyangiitis

Hrs = hours

Hx = history

HUS = hemolytic uremic syndrome

ICU = intensive care unit

KDIGO = Kidney Disease Improving Global Outcomes

MMF = mycophenolate mofetil

MPA = microscopic polyangiitis

NSAIDs = Nonsteroidal anti-inflammatory drugs

pRIFLE = Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease

PUV = posterior urethral valve

RAAS = renin angiotensin aldosterone system

RRT = renal replacement therapy

TFI = total fluid intake

U.O = urine output.

Yrs = years

5. ACUTE KIDNEY INJURY

OVERVIEW

- Acute kidney injury (AKI) is defined functionally as a rapid decline in glomerular filtration rate (GFR) that leads to accumulation of waste products such as blood urea nitrogen (BUN) and creatinine.
- The term acute kidney injury has largely replaced acute renal failure (ARF) because ARF overemphasizes the discrete event of failed kidney function, whereas AKI accounts for a continuum of renal dysfunction that better characterizes the clinical spectrum of AKI.
- AKI has been increasingly recognized as an important complication in hospitalized children.
- AKI occurs in up to 60% of children after cardiac surgery, 10%–80% of all children admitted to an intensive care unit (ICU).
- It is strongly associated with mortality and long-term health consequences.

Definitions of AKI:

- The most important advances in the AKI field would not have been possible without a standardized AKI definition (before 2004, there were >35 definitions).
- Due to lack of a consensus definition, comparisons among studies are difficult, resulting in a wide range of quoted epidemiology, morbidity, and mortality rates in the AKI paediatric literature.
- In 2012, Kidney Disease Improving Global Outcomes (KDIGO) AKI Consensus Conference recommended that the KDIGO AKI definition and staging be used to guide clinical care and as a standardized criterion and outcome measure in AKI as shown in (Table 5.1)

Table 5.1 Modified Kidney disease improving global outcomes (KDIGO) acute kidney injury criteria.

Stage	Serum Creatinine	Urine Output
Stage 0	No change in creatinine or < 0.3mg/dl (26 umol/L)	>0.5ml/kg/hour
Stage 1	1.5–1.9 times baseline OR ≥0.3 mg/dL rise increase (26 umol/L)	<0.5 mL/kg/h for 6–12 hrs
Stage 2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 hrs
Stage 3	3.0 times baseline OR Increase to ≥4.0 mg/dL (>18 yr of age) (>353 umol/L) OR Decrease in eGFR<35 mL/min/1.73m ² (<18 yr. of age) OR Initiation of renal replacement therapy	≤0.3 mL/kg/h for ≥24 hrs OR Anuria for ≥12 hrs

Clinical classification of AKI causes:

- Traditionally, AKI has been classified as:

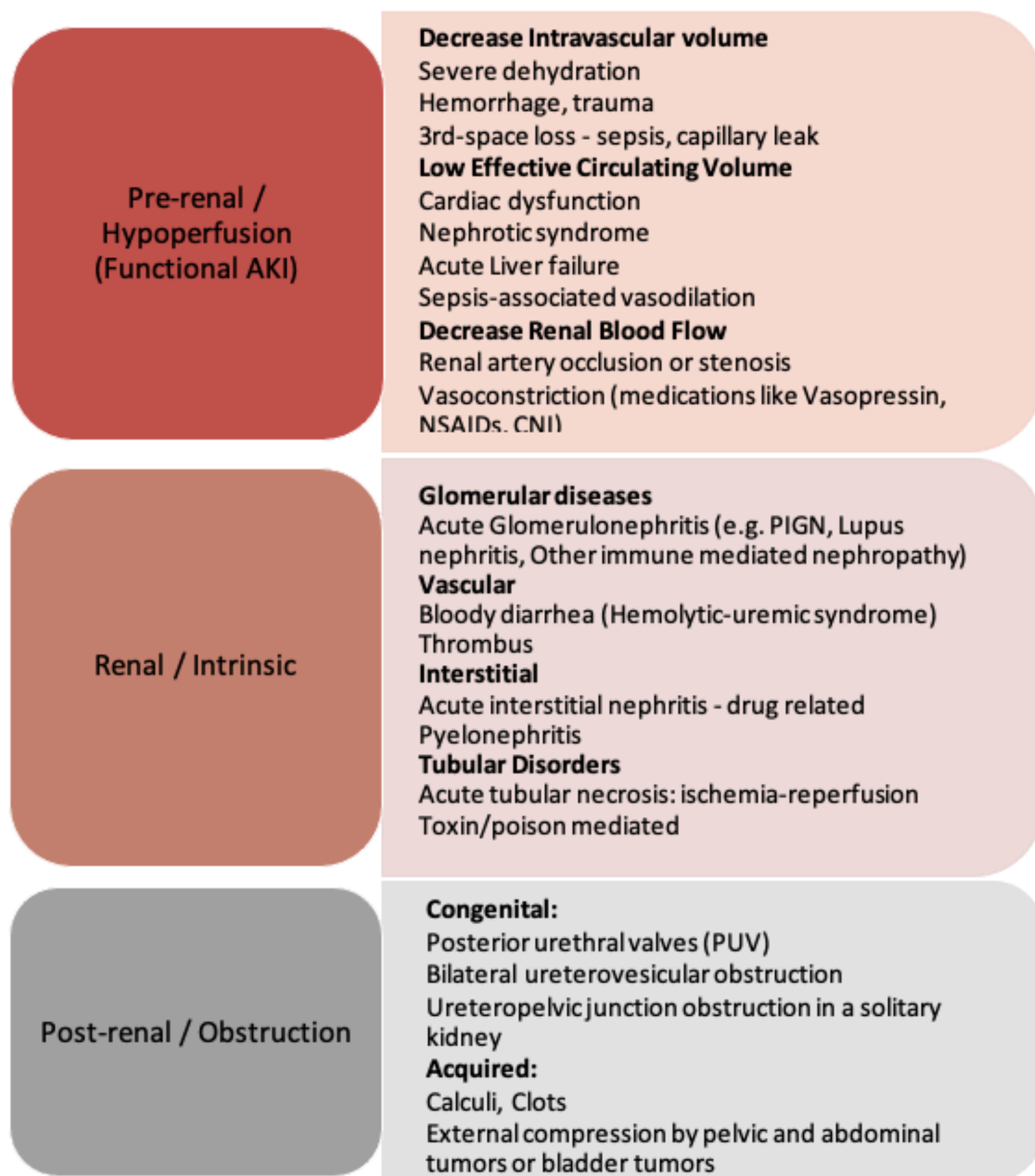


Figure 5.1 Classification of acute kidney injury etiology

ACUTE TUBULAR NECROSIS (ATN)

- Occurs with prolonged and/or severe ischemia which can result in histologic changes, including necrosis, occlusion of the tubular lumen by casts and cell debris.
- It is precipitated by an acute ischemic or toxic event (drugs) or sepsis.

The workup to differentiate acute tubular necrosis from prerenal (functional) AKI and other causes of AKI includes:

1. Urinalysis (UA)

- In prerenal AKI: UA normal or may contain hyaline casts.
- In ATN: UA may show muddy brown casts or tubular epithelial cells secondary to sloughing

2. Fractional excretion of sodium (FENa) = $100 \times [\text{urinary sodium (mmol)} \times \text{serum creatinine (mmol)}] / (\text{serum sodium (mmol)} \times \text{urinary creatinine (mmol)})$

- Pre-renal: less than 1%
- 1-2% FeNa is not conclusive
- ATN/intrinsic renal disease: >2%
- In neonates, FENa >2-3% favours intrinsic kidney disease.
- Not accurate if on diuretics

3. Response to fluid repletion

- In pre-renal: Fluid repletion should cause return of serum creatinine to previous baseline in 24-72 hours
- Persistent AKI despite adequate fluid repletion can represent ATN

DIAGNOSTIC EVALUATION OF AKI

Table 5.2 History and Physical Examination Findings for Categorizing Acute Kidney Injury

Type of AKI	History	Physical Exam
Pre-renal/ Functional	• Volume loss (e.g., history of vomiting, diarrhea, diuretic overuse, hemorrhage, burns, ostomy losses) • Thirst and reduced fluid intake • Cardiac disease • Liver disease	• Weight loss, orthostatic hypotension delayed capillary refill and tachycardia • Poor skin turgor • Dilated neck veins, muffled heart sounds, pulmonary rales, peripheral edema • Ascites, jaundice and other signs of liver failure
Intrinsic renal	• Rash, joint swelling, uveitis, weight loss, fatigue, hematuria, foamy urine, cough, hemoptysis, edema, arthralgia, fever, infectious illness • Trauma, flank pain • Prolonged hypotension • Trauma or myalgia suggesting rhabdomyolysis. • History of receiving nephrotoxic medications (including over-the-counter like NSAIDs, antibiotics (aminoglycosides) and some herbals) • Recent exposure to radiographic contrast agents	• Periorbital, sacral, and lower-extremity edema; rash; hypertension, oral/nasal ulcers, arthritis, fever • Muscle tenderness, high volume status • Hypertension, fundoscopic examination (showing malignant hypertension signs), abdominal bruits • Oliguria/anuria
Post-renal	• Poor urinary stream, history of oligohydramnios, gross hematuria, passing stones, abdominal swelling/mass	• Bladder distention, abdominal/pelvic mass, anuria

Investigations

Initial laboratory tests:

1. CBC, differential count, retic. count.

2. Serum electrolytes, BUN, creatinine with calcium, magnesium, phosphate, bicarbonate level and liver function tests with LDH
3. Coagulation profile
4. Urine tests: urinalysis and microscopy, culture, Protein/Creatinine ratio (PCR), urine electrolytes (Na, K, Cl, creatinine, urea) – FENa can be helpful (as described above)
5. Cultures* (if hx suggests sepsis/HUS): blood, stool cultures are required

Specific laboratory tests:

1. Peripheral blood smear, Coomb's test
2. Immunological work up (if hx suggests immune disease/glomerular disorder): ASO titer, C3, C4, ANA, ANCA (anti-PR3 and anti-MPO), anti-GBM.
3. Drug level for any toxins or nephrotoxic meds and toxicology screen (if history suggest herbal/toxic ingestions)

Imaging

1. Kidney & Bladder ultrasound + doppler (kidney size, presence of hydronephrosis, echogenicity, assess perfusion, rule out thrombosis, assess for reverse diastolic flow).
2. Chest-x-ray (if indicated from the history/Physical exam).

Kidney Biopsy

1. To be ordered by nephrology team if indicated. It is particularly important when clinical assessment and laboratory investigations suggest a diagnosis that requires confirmation before disease-specific therapy (e.g., immunosuppressive medications).

MANAGEMENT OF AKI

- Requires a multidisciplinary team approach with paediatric nephrology expert consultation
- Early discovery of the renal insult
- In general, address the underlying cause (e.g. if post-renal, relief of the obstruction by catheterization/nephrostomy tube)

Management strategies include:

1. Fluid balance

- The fluid status of the child varies depending on the underlying cause, comorbid conditions, and possible previous therapy.
- Monitoring patient condition closely with strict intake & output chart, daily weights, physical examinations (blood pressure and pulse)
- Increase level of monitoring if patient has severe fluid overload.
- Hypovolemia:
 - Fluid therapy given as a normal saline bolus (10 to 20 mL/kg over 30 minutes, repeated after assessment as needed)
 - More invasive monitoring in critical area, such as measuring central venous pressure, may be required to adequately assess the child's fluid status and help guide further therapy.
- Euvolemia:
 - Maintain euvolemia by calculating maintenance fluid requirement.
 - Total fluid intake (TFI) including medications and nutrition = insensible losses [300 to 500 mL/m² BSA per day] + urine and gastrointestinal losses.
 - Formula for BSA

$$BSA(m^2) = \sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}}$$

- Insensible losses can be run as a continuous infusion of D5/NS, with urine output/ GI losses replaced mL:mL with NS. If the patient is able to take fluids by mouth, they could also be advised to drink their insensible losses.
- Hypervolemia:
 - Child with signs of fluid overload may require fluid restriction to insensible fluid [300 to 500 mL/m² per day] if they are anuric.
 - If fluid removal is strongly required like in heart failure or pulmonary edema cases then may need to consider dialysis. % Fluid overload can be helpful in determining need for RRT.
 - Diuretic therapy: a trial of furosemide may be attempted to induce a diuresis and convert AKI from an oliguric to a non-oliguric form, though this might not change the course of AKI.

- Trial of furosemide - single high-dose bolus (2 to 4 mg/kg/dose) to children in the early stages of oliguric AKI with hypervolemia. Stop the furosemide if no response.

2. Electrolytes and acid-base balance

- Hyperkalemia: is the most common electrolyte complication, needs frequent monitoring especially in the oliguric child. Treatment (discussed separately) is based on the severity of hyperkalemia and symptoms present as well as cardiac arrhythmia.
- Hyperphosphatemia and hypocalcemia: Treatment with oral phosphate binders and dietary restriction of phosphorus are commonly used to decrease intestinal absorption of phosphorus.
- Metabolic acidosis: often doesn't require additional treatment and resolves as the AKI resolves.
 - ⊙ May treat metabolic acidosis with IV fluid therapy using lactated ringers' solution or the addition of sodium citrate to enteral fluids, with caution taken to avoid hypocalcemia (alkalosis can lead to decreased ionized calcium)
 - ⊙ Although there is controversy regarding the use of sodium bicarbonate because of its adverse effects, administration of sodium bicarbonate should be considered in life-threatening situations.

3. Hypertension

- Common complication in children with AKI.
- Several contributing factors: fluid overload and renin-mediated hypertension, often seen in children with glomerulonephritis.
- Initial management is typically administration of a diuretic.
- Subsequent management is determined by the severity of hypertension, cause of hypertension, and response to initial therapy
- Typically, ACEi and ARBs are avoided in AKI.

4. Drug management

- Avoidance of nephrotoxic drugs as they may worsen the injury and delay recovery of function
- Dosing adjustment of renally excreted drugs to avoid toxic accumulation of drugs and their metabolites, particularly when GFR has dropped below 50 mL/min/1.73 m²

- Can estimate the GFR based on Bedside Schwartz equation $(36.5 \times \text{ht}(\text{cm})/\text{creatinine } (\mu\text{mol/L}))$, <https://www.mdcalc.com/revised-schwartz-equation-glomerular-filtration-rate-gfr-2009> or, if severe AKI assume GFR is $<10 \text{ mL/min } 1.73 \text{ m}^2$.
- Drug levels should be routinely monitored for medications for which therapeutic monitoring is available (e.g., vancomycin, aminoglycosides, enoxaparin, and digoxin).

5. Renal Replacement Therapy (RRT)

- RRT in children will be discussed in dialysis section of this handbook.

6. Nutritional Support

- AKI is associated with marked catabolism, and optimal nutritional support is crucial to enhance the recovery process.
- If adequate protein and calorie nutrition cannot be achieved because of fluid restriction, RRT should be instituted early in the course of the illness.

Prognosis and outcome

- Many studies report that survivors of paediatric AKI are at risk for chronic kidney disease (CKD) including hypertension and ESRD.
- Long-term follow-up is necessary based on the long-term morbidity for children who survive an episode of moderate or severe AKI.
- It is suggested to follow all children with moderate to severe AKI (stage 2 and above) and those who received renal replacement therapy at least annually for five years, and continued follow-up until adulthood if any evidence of chronic kidney disease (CKD) is detected.

FURTHER READING

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6. APPROACH TO PROTEINURIA

OVERVIEW

Proteinuria refers to loss of protein in the urine. While this may be indicative of kidney damage, the etiology may also be benign. A broad approach to proteinuria, as well as the common causes, are discussed here. Significant proteinuria may present with nephrotic syndrome, which will also be discussed.

How do you measure urine protein? (*See Chapter 2: Diagnostic Tests for details*)

- Urine dipstick
- Spot urine protein-to-creatinine ratio (ensure correct units – generally mg/mmol)

$$\frac{U \text{ protein}}{U \text{ creatinine}}$$

- 24-hour urine protein (gold standard)

MAKING THE DIAGNOSIS

History and Physical Exam

- Thorough history details can be found in History and Physical Exam
- For proteinuria we also specifically ask about:
 - Edema
 - When did it begin? Is the patient symptomatic? (ie. Difficulty breathing, difficulty ambulating, abdominal pain/discomfort)
 - *Hint:* are their eyes puffy in the morning? Have they been diagnosed with “allergies” because of swollen eye lids? Are they finding it hard to get their socks/shoes on? Do they notice an imprint from their socks at the end of the day?
 - This will help assess severity of presentation and guide decision-making around inpatient versus outpatient management
 - The presence of edema suggests non-benign causes of proteinuria

- Ask to see a previous photo of the patient to assess for differences in facial swelling
- Thorough physical exam can be found in *History and Physical Exam*
- For proteinuria we also pay special attention to signs of fluid overload:
 - Vitals
 - Hypertension can be a feature of glomerulonephritis or caused by volume overload in nephrotic syndrome
 - Tachycardia may suggest that the patient is intravascularly volume depleted
 - Documentation of weight gain
 - Fluid status
 - Edema? Where? How clinically significant?
 - Mucus membranes, cap refill time
 - Cardiovascular
 - Gallop may suggest fluid overload
 - Distended JVP for fluid overload
 - Respiratory
 - Crackles for fluid overload, dullness to percussion at bases for pleural effusion
 - Gastrointestinal
 - Tenderness, distension signs of peritonitis, assessment for ascites

General Investigations

- Urinalysis
- Urine protein-to-creatinine (measures all protein)
- Urine albumin-to-creatinine (measures 'glomerular' protein)
- 24-hour urine collection for protein and creatinine that more accurately quantifies the proteinuria (urine creatinine can help to determine if the collection is adequate).
- Serum electrolytes, albumin
- Urea, Creatinine
- If clinically indicated (signs of glomerular disease, other red flags)

- C3/C4
- ANA, dsDNA, hepatitis B and C, HIV
- If presenting with clinical signs concerning for nephrotic syndrome, consider checking serum lipids and cholesterol (although these are not required to confirm the diagnosis of nephrotic syndrome)
- Kidney Ultrasound (confirming presence of 2 kidneys, if additional presence of gross hematuria to rule out thrombosis, helpful for biopsy planning if required)

ETIOLOGIES

Benign Causes of Proteinuria

1. Orthostatic

- Kidney protein excretion increases in the upright position, therefore is more significant as the day progresses
- *Diagnosis:*
 - A first morning urine negative for proteinuria on 3 consecutive days
 - a 'split urine' collection (they fill one container with an entire day's urine starting with their 2nd void of the day, and fill another with the next day's 1st void, then we compare the 'upright' vs 'supine' urine samples)
 - Need to have normal renal function, serum albumin, BP and no hematuria.
- *Management:* Paediatric patients should be reassured, and counselled to collect first-morning specimens for future urine tests as needed

2. Transient

- Temporary proteinuria that occurs in the context of a febrile illness (temperature > 38.3°C), exercise, dehydration, cold exposure, or stress
- *Diagnosis:* Requires repeat urine testing after the acute trigger has resolved to determine if proteinuria is still present.
- *Management:* None, no ongoing monitoring or follow up required once the proteinuria has resolved

Note: every well-appearing child with isolated proteinuria should have multiple first-morning urine samples to rule out the benign causes before moving towards the more extensive work-up for pathologic causes

Non-Benign Causes of Proteinuria

3. Tubular

- Many low molecular weight proteins are reabsorbed in the tubules, therefore damage to the tubules results in urinary loss of these proteins.
- Tubular proteinuria often occurs in the context of generalized tubular dysfunction (Fanconi syndrome), which is typically due to an underlying disease
- Consider disorders that affect the tubules
 - Cystinosis, Dent disease, Lowe syndrome
 - Galactosemia
 - Acute tubular necrosis
 - Tubulointerstitial nephritis
 - Malignancy
 - Congenital anomalies of the kidney and urinary tract (CAKUT)
 - Reflux nephropathy
- *Diagnosis:*
 - Albumin-to-creatinine ratio compared (ACR) to protein-to-creatinine ratio (PCR) may help differentiate glomerular versus tubular proteinuria as albumin is typically lost through the glomerulus while low molecular weight proteins are lost through the tubules
 - You can specifically measure low-molecular weight protein by checking urine beta-2 microglobulin or urine protein electrophoresis
 - Referral to paediatric nephrology may be required to determine underlying diagnosis.
- *Management:*
 - Depends on the underlying etiology.
 - Fanconi syndrome is typically managed by correcting the electrolyte abnormalities. If cystinosis is the diagnosis, cysteamine is part of the therapy.

- Tubulointerstitial nephritis may require a biopsy and subsequent steroid therapy, along with treatment of the underlying cause

4. Glomerular

- Glomerular proteinuria can be divided into nephrotic range which may or may not be associated with nephrotic syndrome, or non-nephrotic range
- Definition of nephrotic range proteinuria:
 - Spot urine PCR greater than 200 mg/mmol (>0.2 g/mmol)
 - 24-hour urine protein greater than 3.5g (or greater than 40 mg/m²/hour)
- The underlying etiology may be a primary kidney condition or secondary to a systemic/non-kidney condition
- Isolated Proteinuria:
 - Minimal change disease
 - Most common cause of nephrotic syndrome in children
 - Focal segmental glomerular sclerosis
 - FSGS is a histological pattern of kidney injury, it's not in itself a diagnosis
 - It may be idiopathic (this is typically related to some immune dysregulation leading to an FSGS injury pattern, and can cause mild proteinuria up to a full nephrotic syndrome)
 - FSGS can also be secondary to infection (hepatitis B, C, HIV among others), autoimmune disease, drugs, malignancy, or chronic hyperfiltration (e.g. obesity, hypertension, heart failure)
 - Membranous nephropathy (rare in kids)
 - MN is also a histological pattern of injury that may be caused by infection, autoimmune disease, malignancy, and drugs
 - Primary (related to phospholipase A2 receptor antibodies (PLA2R)) or secondary
 - Diagnosed on biopsy
 - It can also be seen (very rarely) in neonates due to circulating auto-antibodies
 - Treatment dependent on underlying etiology or degree of proteinuria level of kidney impairment. May consider prednisone, or tacrolimus/calcineurin

inhibitor if severe. Renin angiotensin aldosterone system (RAAS) blockade indicated.

- Proteinuria with Hematuria (See section on hematuria)
 - Post-infectious glomerulonephritis
 - Membranoproliferative glomerulonephritis/C3 glomerulopathy
 - Can present with varying severities of nephrotic syndrome and/or glomerulonephritis
 - IgA Nephropathy
 - Typically presents with hematuria, but can involve proteinuria
 - Glomerulonephritis (Henoch-Schonlein purpura (IgA vasculitis), lupus nephritis, ANCA, anti-GBM disease)
 - Alport syndrome
- Diagnosis is by clinical and biochemical findings, more definitively by kidney biopsy.
- Management dependent on the underlying etiology
 - Consider using an ACE inhibitor (or ARB) to help to reduce the proteinuria (RAAS blockade)

Nephrotic syndrome

1. Nephrotic range proteinuria
2. Hypoalbuminemia
3. Edema
4. $\pm$ Hyperlipidemia (not always required for diagnosis)

Summary of urinary protein interpretation

	NORMAL	ABNORMAL	NEPHROTIC RANGE
Urine dipstick	Negative–trace	1+ or 2+	3+ or 4+
Urinalysis	<0.3 g/L	0.3–3 g/L	>3 g/L
Protein creatinine ratio (PCR)	<25 mg/mmol	25–200 mg/mmol	>200 mg/mmol

Figure 6.1 Image from BC Children's Nephrotic Syndrome Physician Handbook)

Please note, some centres use g/mmol as their screening units, therefore normal urine PCR = <0.02 g/mmol, abnormal would be 0.02 – 0.2 g/mmol, and nephrotic range would be >0.2 g/mmol)

Patients with uncomplicated nephrotic syndrome may be managed by general pediatrics, however if there are any concerns for complicated features, they should be assessed by a paediatric nephrologist. Various factors will be considered when determining whether management should be as an inpatient or outpatient.

The most likely diagnosis in paediatrics is minimal change disease, and this is often a presumptive diagnosis (even without biopsy).

You should consider other diagnoses (and biopsy) if:

- The patient is under 1 or over 12 years old
- There is gross hematuria (not related to renal vein thrombosis)
- They are hypertensive
- They have abnormal kidney function (e.g. low eGFR) not pre-renal in nature
- C3 is low
- There is evidence of systemic disease (e.g. arthritis or rashes)
- They are steroid-resistant
 - Defined by the persistence of proteinuria after 4 weeks of steroid therapy (see management below)

MANAGEMENT & FOLLOW UP

Acute Symptomatic Management

- Is the patient presenting with signs of volume overload (hypertension, edema) or intravascular volume depletion (ie. Tachycardia, elevated creatinine, edema)?
 - May consider diuretics; this should be discussed with a nephrologist
 - Fluid and salt restriction (one example in the table below)
 - Consideration of 25% albumin infusion if pre-renal or presence of anasarca

- FeNa may be helpful to determine if will respond to diuretics alone or need albumin and diuretic
- Is the patient hypertensive?
 - How significant is it and are they symptomatic?
 - Consider diuretics if volume overloaded, and possibly short-acting anti-hypertensives
- Considerations for admission:
 - Volume overload or depletion requiring IV management
 - Severe, symptomatic edema (i.e. significant ascites, pleural effusions)
 - Symptomatic hypertension may require admission
 - Concerns of acute complications (discussed below)

Recommended maximum calorie, sodium, and fluid intake

WEIGHT (kg)	CALORIE AND SODIUM (mg/day)*		FLUID (ml/day)**
	BOYS	GIRLS	
10	800	800	500
20	1,300	1,300	750
30	1,600	1,400	900
40	1,700	1,600	1,000
50	2,000	1,700	1,100
60	2,300	1,800	1,100
70	2,400	1,900	1,200

* While on prednisone ** While in relapse

Figure 6.2 An example of Fluid/Salt restriction, from BC Children's Nephrotic Syndrome Physician Handbook

Acute Complications

- Consider the most serious complications of nephrotic syndrome:
 - Thromboembolism: Pathophysiology is multifactorial, however the loss of anti-thrombotic protein and protein S, in addition to increased hepatic synthesis of pro-thrombotic factors are thought to play a role
 - Spontaneous bacterial peritonitis: stagnant fluid collection in abdomen is prone to infection (particularly by *Streptococcus pneumoniae*).

- Infection: Multifactorial pathophysiology including urinary losses of proteins involved in the complement pathway,
 - If there are concerns (i.e.. Fever) culture and start empiric antibiotics covering for pneumococcus (*Streptococcus pneumoniae*) and gram-negative bacteria (predominantly *Escherichia coli*)

Disease Management

- These patients are followed by paediatric nephrology long-term (depending on the centre, nephrology may only follow complicated cases of nephrotic syndrome)
 - Oral steroids are the typical starting therapy for **new onset** nephrotic syndrome
 - Generally started at 60 mg/m²/day (or 2 mg/kg/day) for 6 weeks, then tapered per local institutional protocols until discontinued
 - Example of taper schedule:
 - Step 1:** 60 mg/m²/day daily for 6 weeks
 - Step 2:** 40 mg/m²/day every other day for 6 weeks, then off
 - Parents check urine daily at home to monitor proteinuria and response to therapy

Long-Term Management

- 70-75% of children will relapse and require re-treatment with steroids (usually not as long)
- If frequently relapsing (2 or more episodes in 6 months, 4 or more in 12 months) consider low-dose maintenance steroids or second-line immunosuppressive medications (such as cyclophosphamide, tacrolimus, mycophenolate, rituximab, levamisole). Occurs in up to 50% of children.
- If steroid dependent (unable to wean or discontinue steroids) consider low-dose maintenance steroids or second-line immunosuppressive medications
- If steroid resistant (unable to achieve remission after 4-6 weeks of steroids) then plan kidney biopsy. Management will be dependent on biopsy results. Often may use second line immunosuppressive medications and consider genetic testing.
- In these cases, referral to paediatric nephrology should be initiated if not already done

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7. HYPERTENSION IN CHILDREN

OVERVIEW

- Prevalence of hypertension (HTN) among healthy children and adolescents is 3.5%-5%.
- However, prevalence of HTN in various comorbid conditions children is much higher: 3.8-25% in obesity, 3.6-14% in children with obstructive apnea, 50% in those with chronic kidney disease and 7-10% in children with prematurity.

Importance of Diagnosing HTN in Children and Adolescents

- Elevated BP in childhood increases the risk for adult HTN and metabolic syndrome.
- BP-related cardiovascular damage starts in youth.
- Early detection of HTN is vital to prevent future cardiovascular morbidity and mortality

Definition of HTN

- BP levels in children should be interpreted based on sex, age, and height. **New normative BP tables** based on normal-weight children have been introduced by the American Academy of Pediatrics.
- Hypertension in children is defined as a BP $\geq$ 95th percentile for age, sex, and height (in children 1-12 years) or $\geq$ 130/80mmHg (in children $\geq$ 13 years) on 3 separate consecutive occasions.
- **Hypertension Canada definition:** children can be diagnosed as hypertensive if systolic or diastolic BP is at the 95th percentile or greater for age, sex, and height, measured on at least 3 separate occasions, or if systolic or diastolic BP is $>$ 120/80 mm Hg in children 6-11 years of age, or greater than 130/85 mm Hg in children 12-17 years of age

Figure 7.1. Blood pressure categories and definitions

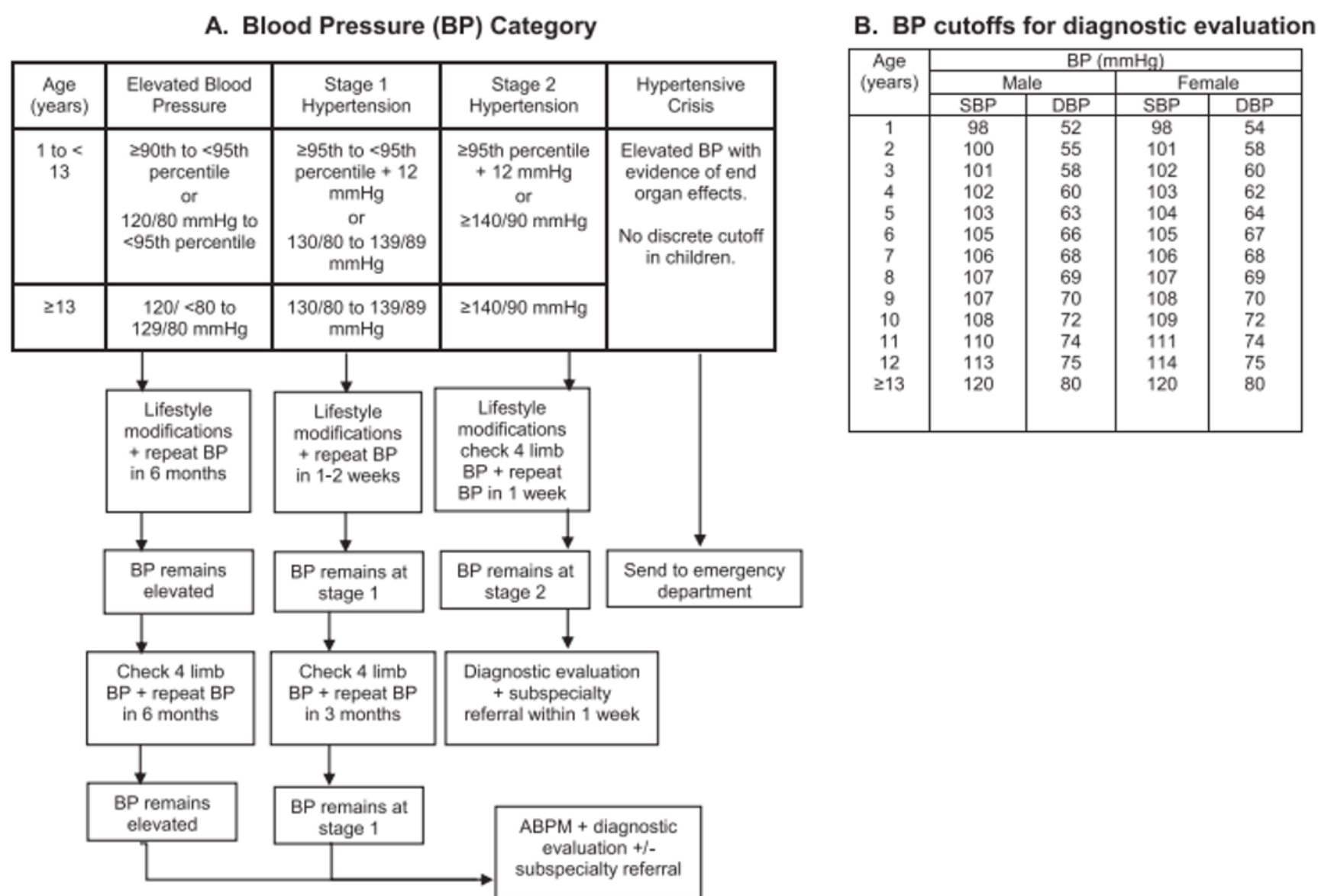


Figure 1. (A) Blood pressure (BP) categories and definitions. The lowest cut-off in each category should be used to make a diagnosis as outlined in the algorithm (5). If BP normalizes at any point, return to annual screening. (B) Shows the minimum systolic and diastolic BP that warrants further investigation for girls and boys, based on age (5).

Figure used with permission from Saini P, Betcherman L, Radhakrishnan S, Etoom Y. Paediatric hypertension for the primary care provider: What you need to know. *Paediatrics & Child Health*. 2021 Apr;26(2):93-8.

Measurement of BP in Children

- It is important to obtain multiple measurements over time before diagnosing HTN.
- The initial BP measurement may be oscillometric (on a calibrated machine that has been validated for use in the paediatric population) or auscultatory (by using a mercury or aneroid sphygmomanometer) .
- An appropriately sized cuff should be used for accurate BP measurement. the initial BP is elevated (≥90th percentile), providers should perform 2 additional oscillometric or auscultatory BP measurements at the same visit and average them.

- If using auscultation, this averaged measurement is used to determine the child's BP category. If the averaged oscillometric reading is ≥ 90 th percentile, 2 auscultatory measurements should be taken and averaged to define the BP category.

BP Measurement Frequency

- Guidelines recommend annual BP screening for healthy children aged 3 and above
- Some children should have BP measured before 3 years and at every health encounter:
 - obesity (BMI ≥ 95 percentile)
 - kidney disease
 - diabetes
 - aortic arch obstruction or coarctation
 - those who are taking medications known to cause HTN
 - prematurity

ABPM (Ambulatory BP Monitoring)

- ABPM is more accurate for the diagnosis of HTN than clinic-measured BP, is more predictive of future BP, and can assist in the detection of secondary HTN.
- For these reasons, the routine application of ABPM is recommended, when available.
- For technical reasons, ABPM may need to be limited to children ≥ 5 years of age who can tolerate the procedure and those for whom reference data are available.
- ABPM is indicated in the following scenarios:
 - Confirmation of the diagnosis of hypertension in children with repeatedly elevated office BP readings
 - Confirmation of suspected white coat hypertension
 - Evaluation for masked hypertension in children
 - Evaluation of BP in paediatric transplant recipients, children with CKD and children on dialysis
 - Assessment of treatment effectiveness in children and adolescents receiving antihypertensive medications

ETIOLOGIES

Primary HTN

- Primary HTN is now the predominant diagnosis for hypertensive children and adolescents.
- General characteristics of children with primary HTN include a) older age (≥ 6 years), b) positive family history (in a parent and/or grandparent) of HTN, and c) overweight and/or obesity.
- Children and adolescents ≥ 6 years of age do not require an extensive evaluation for secondary causes of HTN if they have a positive family history of HTN, are overweight or obese, and/or do not have history or physical examination findings suggestive of a secondary cause of HTN.

Secondary HTN

- Children < 6 years of age are more likely to have a secondary cause for their hypertension
- Causes of secondary hypertension include:
 - Renal (renovascular and renal parenchymal disease, congenital abnormalities)
 - Cardiac (coarctation of aorta)
 - Respiratory (chronic lung disease-bronchopulmonary dysplasia)
 - Iatrogenic (medication, fluid overload)
 - Oncological (e.g. neuroendocrine tumours)
 - Systemic (e.g. prematurity)
 - Endocrine (e.g. hyperthyroidism, Cushing syndrome)

Renal Causes

- Renal disease and renovascular disease are among the most common secondary causes of HTN in children.
- Renal parenchymal disease and renal structural abnormalities account for 34% to 79% of patients with secondary HTN. Common causes are acute glomerulonephritis, interstitial nephritis, renal scarring, obstructive nephropathy, polycystic kidney disease, etc.)

- It is appropriate to have a high index of suspicion for renal and renovascular disease in hypertensive paediatric patients, particularly in those <6 years of age, or teenagers with low BMI if no other risk factors, particularly with stage 2 hypertension.
- Causes of renovascular disease can be fibromuscular dysplasia (FMD), Takayasu arteritis (TA), mid-aortic syndrome.
- Renovascular HTN should be suspected in the following scenarios:
 - Unexplained hypokalemia with or without high renin
 - Sustained diastolic HTN on ABPM
 - Clinic BP >150/100 at any age
 - Hypertension not controlled on ≥ 2 antihypertensive drugs
 - Increase in creatinine (if bilateral renovascular disease) with ACE inhibitor initiation
 - Stage 2 HTN in <10 y/o child
 - Genetic syndrome associated w/renovascular hypertension
 - Known vasculitis or symptoms of vasculitis
 - History of renal trauma or vascular insult
 - Mid-abdominal bruit on PE
 - Severe HTN post-transplant
 - Symptomatic HTN w/o defined cause

DIAGNOSTIC EVALUATION OF HTN

Table 7.1 History, physical and targeted investigations.

Table 1. History, physical, and targeted investigations, organized by system to assess the etiology of hypertension		
Cause	Clues from history and physical exam	Possible investigations
Primary hypertension	>6 years with: - Primary hypertension in a parent or grandparent - Overweight/obese - No suspicion for alternative cause	- Lipid profile - Electrolytes (sodium, potassium, chloride, bicarbonate) - Creatinine, BUN - UA - HbA1C, fasting glucose
Renovascular and renal (structural or glomerular abnormalities)	- Hematuria, edema, oliguria	- UA, electrolytes, BUN, creatinine , urine albumin: creatinine ratio - CBC - Renal US* - Renal US with Doppler**
Endocrine (hyperthyroidism, Cushing disease, type 2 diabetes mellitus, pheochromocytoma)	- Palpitations, tremors, sweating, headache - Acne, hirsutism, pubertal abnormalities - Family history of endocrine disease - Tachycardia	- TSH - HbA1C, fasting glucose - ACTH - Plasma and/or urine metanephrine/normetanephrine
Cardiac (aortic coarctation)	- Abnormal pulses - Upper + lower limb BP discrepancy	- Echocardiogram***
Respiratory (obstructive sleep apnea)	- Abnormal breathing during sleep - Tonsillar hypertrophy - Morning headaches, daytime fatigue	- Polysomnography
Genetic (Neurofibromatosis, Turner's syndrome)	- Dysmorphic features	- Genetic testing
Medication	- History of herbal supplements, prescription or illicit drug use, or vitamins	- Drug screen

Table used with permission from Saini P, Betcherman L, Radhakrishnan S, Etoom Y. Paediatric hypertension for the primary care provider: What you need to know. *Paediatrics & Child Health*. 2021 Apr;26(2):93-8.

Imaging

1. ECG: no role of ECG in HTN in children
2. Echo: Necessary for identifying end organ damage such as LVH
 - Timing: Start of pharmacologic treatment of HTN, though Canadian guidelines advise an echocardiogram for all cases

- Repeat echocardiography performed to monitor improvement at 6- to 12-month intervals
3. Ultrasound kidney with doppler is recommended for children especially <6 years of age with hypertension (Should be done in all children before starting ACE inhibitor/ARB)
 4. CT or MR angiography can also be used as they are non-invasive. Sensitivity and specificity for the detection of RAS is 94% and 93% for CTA and 90% and 94% for MRA, respectively.
 5. Digital subtraction angiography (DSA) is the most reliable way to diagnose renal artery stenosis (RAS)

MANAGEMENT & FOLLOW UP

In children and adolescents diagnosed with HTN, the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to <90th percentile and <130/80 mm Hg in adolescents $\geq$ 13 years old.

Lifestyle and Nonpharmacologic Interventions

- Dietary Approach to Stop Hypertension diet (DASH): 4-5 servings of fruit and vegetables per day, >2 servings of low-fat milk products, 6 servings of whole grains, <2 servings of fish/poultry and lean red meats, 1 serving of legumes and nuts, 2-3 servings of oils and fats, avoiding added sugar and sweets, and dietary sodium <2300 mg/day
- Recommend moderate to vigorous physical activity at least 3 to 5 days per week (30–60 minutes per session) to help reduce BP.

Pharmacologic Treatment

- Pharmacologic treatment of HTN in children and adolescents should be initiated with an ACE inhibitor, ARB, long-acting calcium channel blocker, or a thiazide diuretic. β -blockers are not recommended as initial treatment in children.
- Common side effects of some of the medications include:
 - Calcium Channel Blocker (e.g. Amlodipine): peripheral edema
 - ACE inhibitor/ARB: hyperkalemia, increased creatinine. Cough and angioedema are more common in adults. Adolescent patients should be counselled about teratogenic effects in pregnancy.

- Diuretics: Electrolyte disturbances
- β -blockers: bradycardia, hypoglycemia. Should be avoided in patients with asthma.
- Depending on repeated BP measurements, the dose of the initial medication can be increased every 2 to 4 weeks until BP is controlled (eg, <90th percentile), the maximal dose is reached, or adverse effects occur.
- Although the dose can be titrated every 2 to 4 weeks using home BP measurements, the patient should be seen every 4 to 6 weeks until BP has normalized.
- If BP is not controlled with a single agent, a second agent can be added to the regimen and titrated as with the initial drug.
- Lifestyle modifications should be continued in children requiring pharmacologic therapy.
- In children with HTN and CKD, proteinuria, or diabetes mellitus, an ACE inhibitor or ARB is recommended as the initial antihypertensive agent unless there is an absolute contraindication.

Figure 7.2. Patient management based on office BP

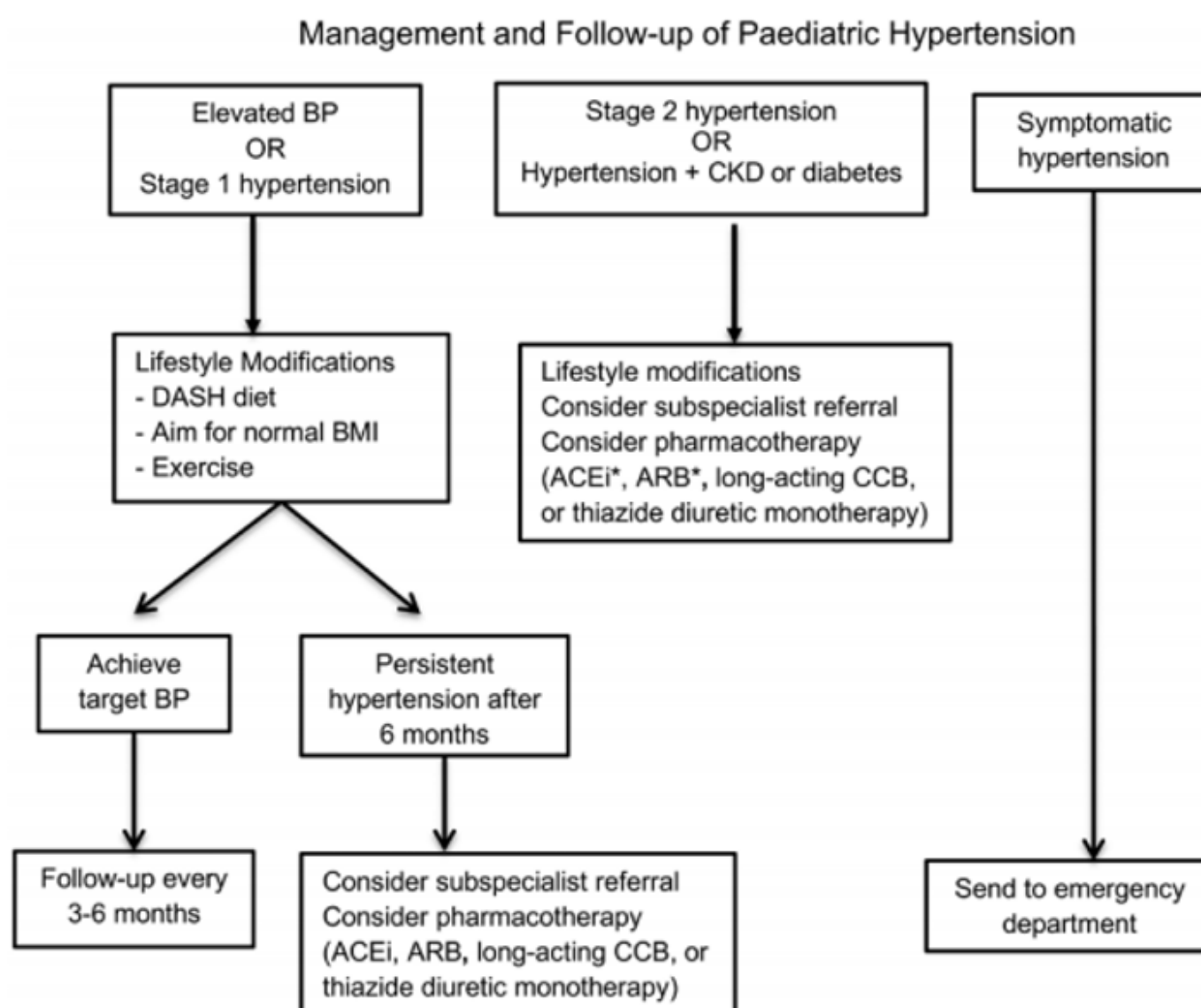


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HYPERTENSION IN HOSPITALIZED CHILDREN

- Paediatric HTN has been well studied in the ambulatory setting but not so much in hospitalized children
- Lack of robust inpatient BP data
- Significance of an elevated BP and the cut-off at which elevated BP evolve into true HTN is not entirely clear
- First step is to rule out pain, anxiety, fluid overload etc.
- Treatment should be considered:
 - Acutely in hospitalized patients who have sustained stage 2 HTN that persists for greater than a day
 - Children experiencing a sudden rise in BP, regardless of whether or not it meets the stage 2 threshold
 - Any patient with hypertensive emergency or encephalopathy should be treated immediately in an ICU setting
 - Children at greater risk for seizures or encephalopathy
 - Those at a greater risk for hypertensive complications (recent surgery, thrombocytopenia, etc.), should be treated at lower thresholds
 - Hypertensive emergency: BP elevation is accompanied by evidence of severe symptoms and end-organ damage
 - Hypertensive urgency: Minimal end organ damage
- Hypertensive emergency/urgency have BP >stage 2 hypertension threshold (when child's BP increases 30 mmHg or more above the 95th percentile)
- This corresponds to a SBP of above 160 mmHg in children 13 years and older or above 135 mmHg in a 1-year-old child

ACUTE SEVERE HYPERTENSION

Hypertensive emergencies should be treated in an ICU setting with titratable IV antihypertensive medications. In such situations, the BP should be reduced by no more than 25% of the planned reduction over the first 8 hours, with the remainder of the planned reduction over the next 12 to 24 hours. The ultimate short-term BP goal in such patients should generally be around the 95th percentile.

Treatment options:

- IV hydralazine
- IV labetalol
- IV nitroprusside
- IV nicardipine
- PO nifedipine

FURTHER READING

Dionne et al. Hypertension Canada Guideline Committee. Hypertension Canada's 2017 Guidelines for the Diagnosis, Assessment, Prevention, and Treatment of Pediatric Hypertension. *Can J Cardiol*. 2017 May;33(5):577-585. doi: 10.1016/j.cjca.2017.03.007. Epub 2017 Mar 14. PMID: 28449829.

Flynn et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017 Sep;140(3)

Flynn et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. *Hypertension*. 2014 May;63(5):1116-35

Lurbe et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens*. 2016 Oct;34(10):1887-920

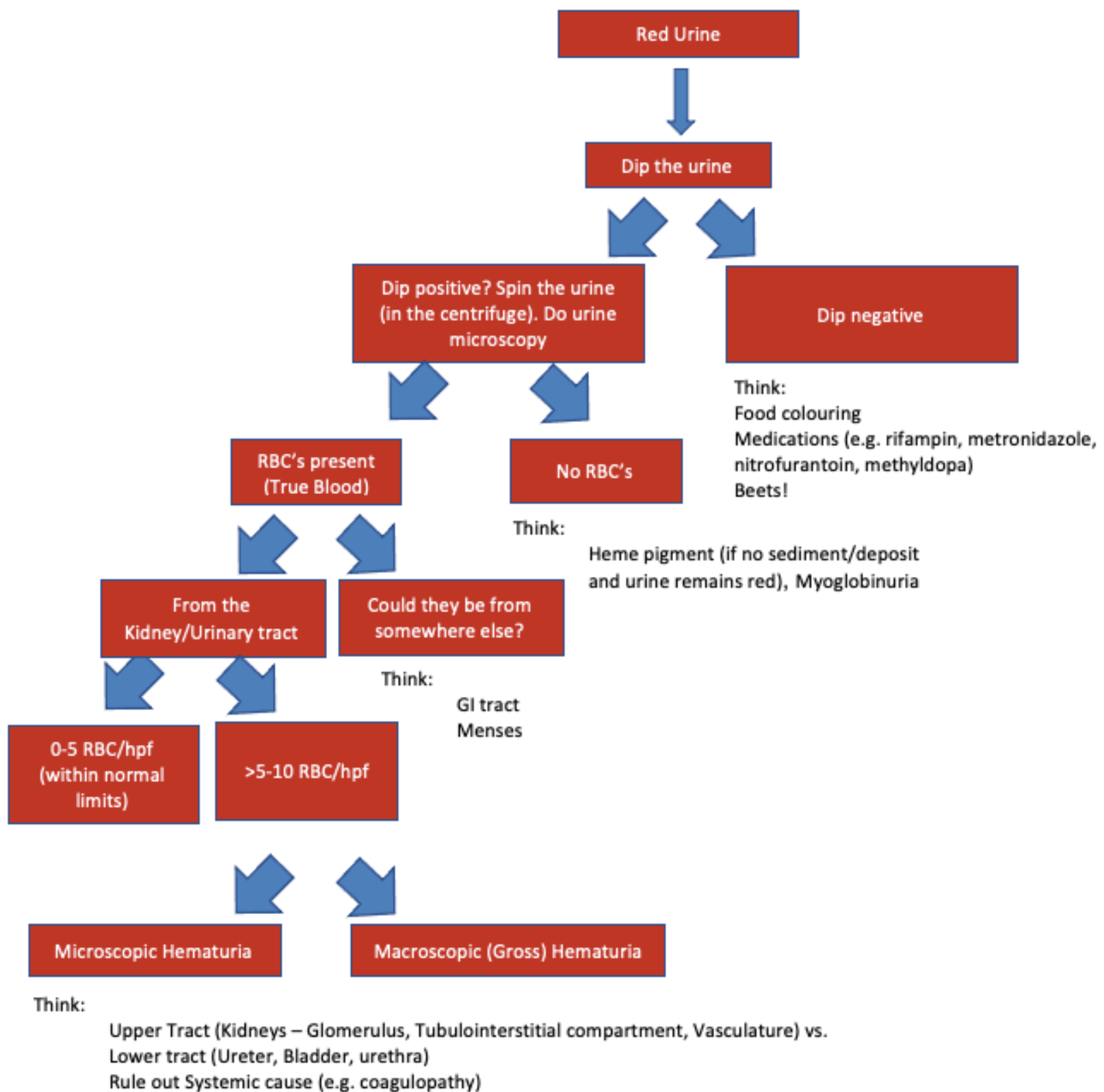
Rabi et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Canadian Journal of Cardiology* 36 (2020) 596-624

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8. APPROACH TO HEMATURIA/ GLOMERULONEPHRITIS

OVERVIEW

An approach to red-coloured urine:



- Transient hematuria can be associated with exercise, fever

- Persistent microscopic hematuria requires further investigation
- Once you have proven there is true hematuria, then the next step is to establish upper urinary tract vs. lower urinary tract cause. Here are some clues below:

Table 8.1. Upper vs. Lower Urinary Tract causes of hematuria

Upper Urinary Tract (Renal)	Lower Urinary Tract
Cola-coloured, tea-coloured	Bright-pink/red, may have clots
May/may not be associated with pain	May be associated with pain
Dysmorphic RBC's, RBC casts	RBC shape normal
Associated with proteinuria	Generally no proteinuria

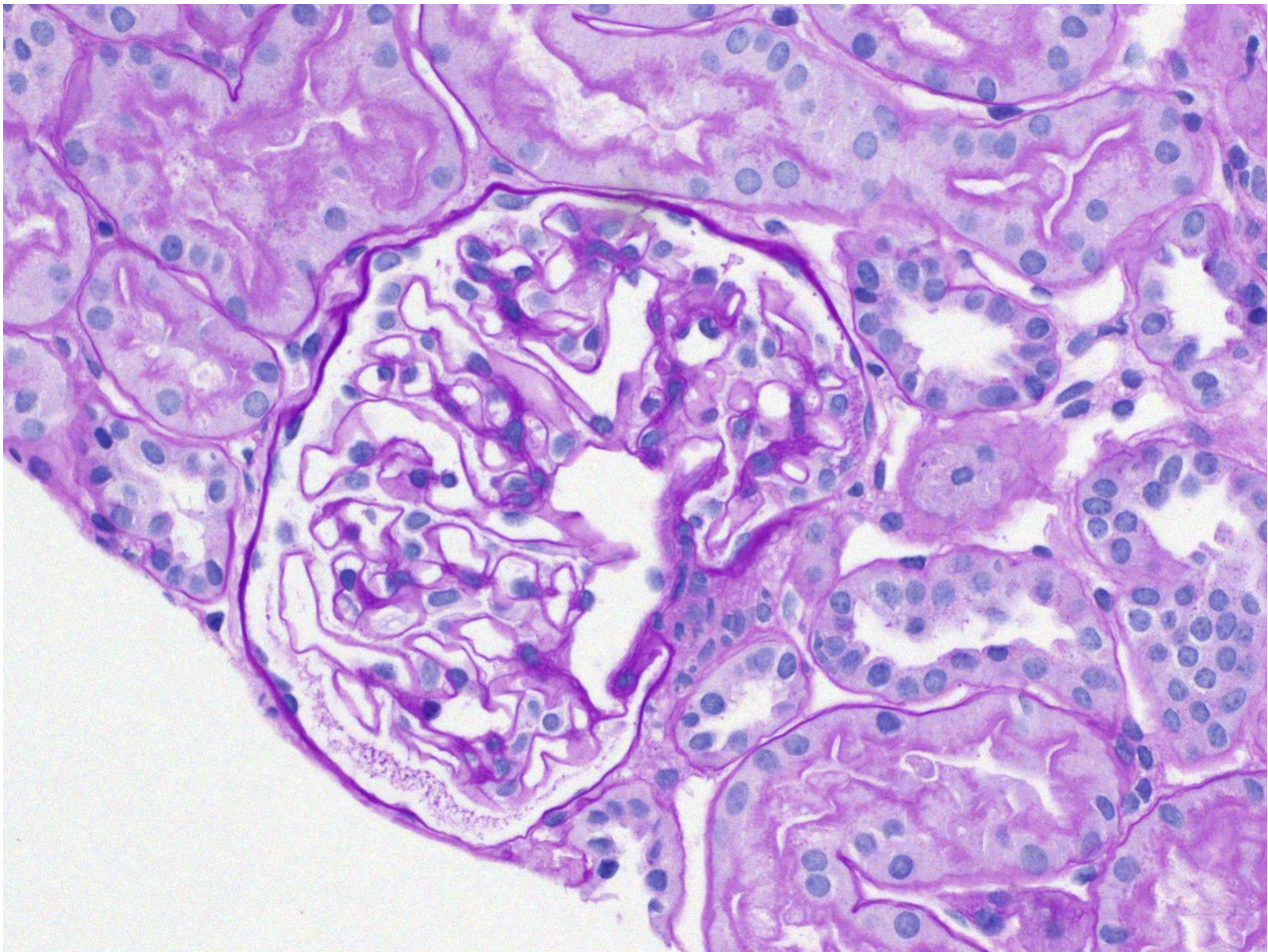


Figure 8.1. A normal glomerulus. (Periodic Acid Schiff (PAS), X200). Image courtesy of Dr. Rose Chami.

UPPER URINARY TRACT (RENAL) CAUSES

- For a systematic approach, can divide upper urinary tract into 3 compartments – Glomerulus, Tubulo-interstitial, and Vasculature

Glomerulus - Glomerulonephritis

- Use the C3 rule! See table below.
- Causes of hematuria can include: post-infectious glomerulonephritis, C3 glomerulopathy, Lupus nephritis, IgA nephropathy, thin-basement membrane disease, Alport syndrome, anti-glomerular basement membrane disease, vasculitis (ANCA-associated, including Granulomatosis with polyangiitis), and more

Tubulo-interstitial

- Acute tubular necrosis, Tubulointerstitial nephritis (medication-related)

Vasculature

- Renal vein thrombosis, Renal artery thrombosis, Nutcracker syndrome

Glomerulonephritis

Making the Diagnosis:

- Definition of GN: triad of gross hematuria (with red cell casts), edema, and hypertension (salt and water retention). Additional features can include acute kidney injury (oliguria, uremia, elevated creatinine) and proteinuria.
- For glomerular causes, use the C3 rule – Low C3 vs. Normal C3, and Renal-limited vs. Systemic disease

Table 8.2 Guide to differential diagnosis of glomerulonephritis using C3.

	Renal-Limited	Systemic Disease
Low C3	• Post-infectious Glomerulonephritis • C3 glomerulopathy (previously known as Membranoproliferative Glomerulonephritis)	• Lupus Nephritis (C4 usually low too, can rarely be renal-limited) • Shunt nephritis • Endocarditis
Normal C3	• IgA nephropathy • Thin-basement membrane disease • Anti-Glomerular basement membrane (Anti-GBM) disease	• Alport Syndrome • Henoch-Schönlein Purpura (IgA Vasculitis) • Goodpasture syndrome (pulmonary-renal anti-GBM disease)

*ANCA-associated vasculitis (E.g. Granulomatosis with polyangiitis) can present in all 4 categories

- GN workup would include:
 - Initial screen: CBC, Electrolytes, Calcium/Magnesium/Phosphate, urea, creatinine, albumin, C3, C4, ASOT
 - Consider: HIV, Hep B/Hep C, ANA, ANCA, Anti-dsDNA
 - +/- kidney biopsy if proteinuria/acute kidney injury/hypertension/other red flags
 - See clinical features and diagnosis/management plan for key conditions below.

Post-Infectious Glomerulonephritis

Clinical Features

- Most common cause of acute nephritis worldwide
- Most common cause is post-Group A streptococcal infection with nephritogenic strains, but can also be secondary to other bacterial (*Staphylococcus aureus*, *Mycoplasma pneumonia* etc.), viral, fungal and parasitic infections
- Preceding URTI with Group A beta-hemolytic Strep usually 1-2 weeks before GN, or skin infection up to 3-6 weeks before GN
- Pathophysiology: Group A strep antigen deposition (nephritis-associated plasmin receptor/streptococcal pyrogenic exotoxin B) with in-situ immune complex formation

- Immune complex formation leads to complement deposition, mesangial proliferation and leukocyte infiltration
- Tea/Cola-coloured urine (1/3 of patients), proteinuria, oliguria and hypertension
- If creatinine is rising rapidly, nephrotic range proteinuria – could be indicative of a rapidly progressive glomerulonephritis (crescentic GN)

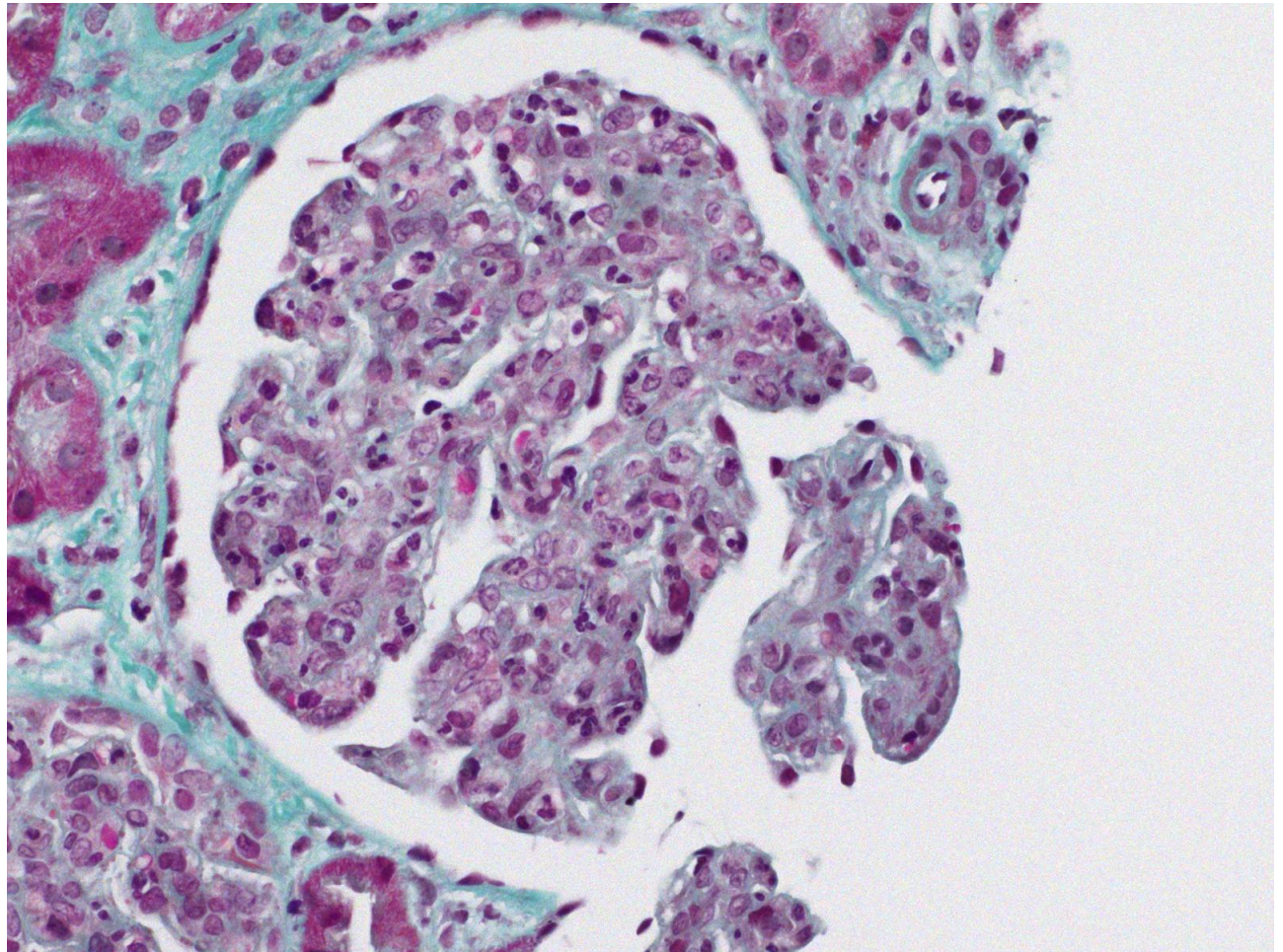


Figure 8.2. Acute PIGN – acute diffuse proliferative glomerulonephritis. A glomerulus with global endocapillary hypercellularity with numerous neutrophils and closure of the glomerular capillaries. (Masson's trichrome, x200). Image courtesy of Dr. Rose Chami.

Diagnosis

- Initial GN screen should be completed
- Hallmark - Low C3! With normal C4
- Anti-streptolysin-O-titre (especially in pharyngeal infections, but not in skin infections) – serial measurements more helpful, and anti-DNAse B antibody can also be checked. This can confirm if Strep was present, but is not required for diagnosis of PIGN
- Throat culture can be helpful if at time of acute infection
- If unusual features, rapidly rising creatinine – perform renal biopsy.
- Biopsy features: enlarged glomeruli, increased cellularity and infiltration of neutrophils, Immunofluorescence positive for C3, IgG +/- IgM, classically subepithelial “humps” on electron microscopy, representing immune complex deposits

Management

- Supportive, 1% of patients will require dialysis
- Fluid & salt restriction to control blood pressure and edema, +/- furosemide for hypertension management and other anti-hypertensive medication can be considered
- In rapidly progressive GN, could consider immunosuppression, very rarely used (i.e. pulse methylprednisolone)
- Treat Strep infection to prevent spread of strain but this will not prevent nephritis in patient or modify the course
- Initial gross hematuria can last up to 10 days, microscopic hematuria can persist up to 1-2 years
- C3 should be back to normal at 6-8-week mark. If not, consider renal biopsy for C3 glomerulopathy, or other cause
- PIGN should not recur (only rare case reports of recurrence). If gross hematuria returns, consider another diagnosis.
- <1% progress to ESRD

C3 Glomerulopathy (C3G)

Clinical Features

- Previously known under the umbrella of membranoproliferative glomerulonephritis (MPGN) – Type 1, 2, 3 (based on where deposits were found on electron microscopy)
- Now pathophysiology recognized due to dysregulation of complement pathway
- Key presenting feature is low C3 (which persists beyond 6-8 weeks)

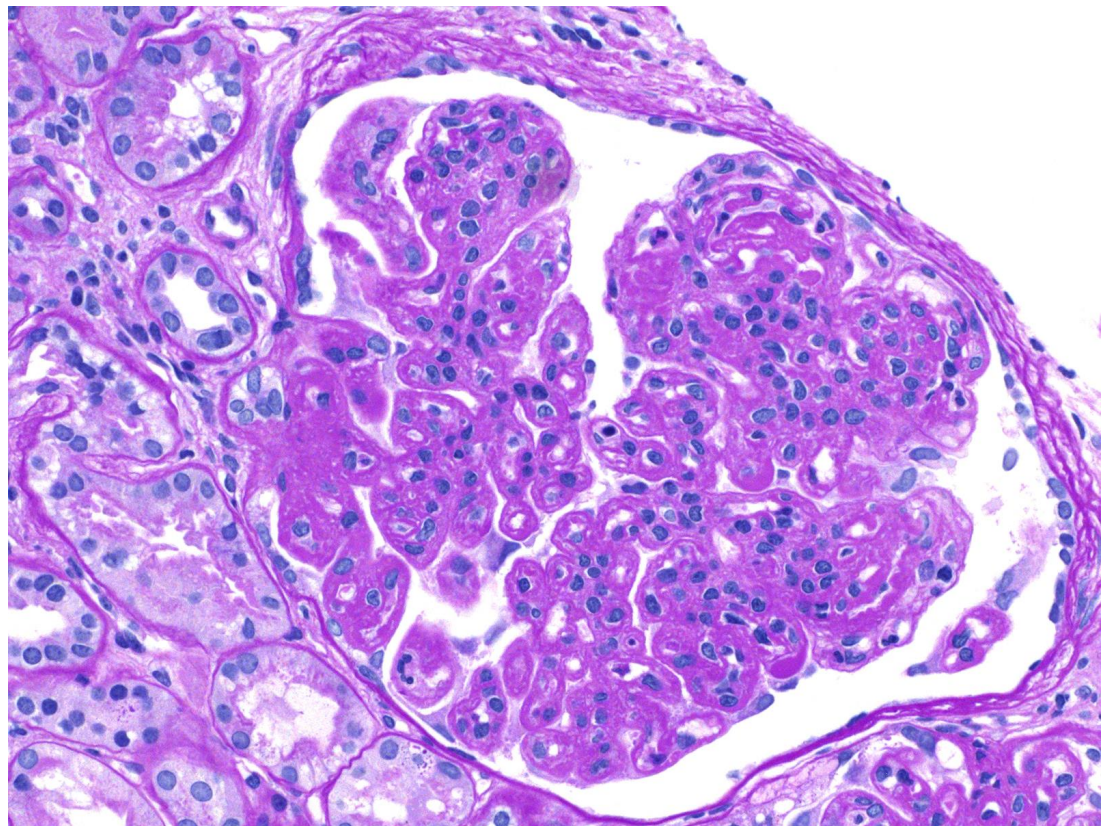


Figure 8.3. C3 glomerulonephritis – MPGN pattern. A glomerulus with exuberant mesangial hypercellularity, which gives a lobulated appearance and capillary wall thickening with double contour formation. (PAS, X200) Image courtesy of Dr. Rose Chami.

- May include proteinuria (non-nephrotic AND nephrotic range), microscopic/gross hematuria, edema, hypertension, increased creatinine

Diagnosis

- Made by renal biopsy, classification system based on renal biopsy findings
- Membranoproliferative glomerulonephritis on light microscopy
- Immunofluorescence – exclusive or predominant C3 deposits (C3 glomerulonephritis and Dense Deposits Disease) vs. complement AND immunoglobulin deposits (Immunoglobulin-mediated MPGN)
- C5b9 deposits in the kidney (membrane attack complex)
- For immunoglobulin-mediated MPGN – rule out secondary causes i.e. autoimmune disease (systemic lupus erythematosus, Sjogren syndrome, mixed connective tissue disease), infections (HIV, Hep C, endocarditis), cirrhosis, Sickle cell anemia
- Do a complement workup – genetic testing as well as biochemical functional assay to look for autoantibodies to complement regulatory proteins

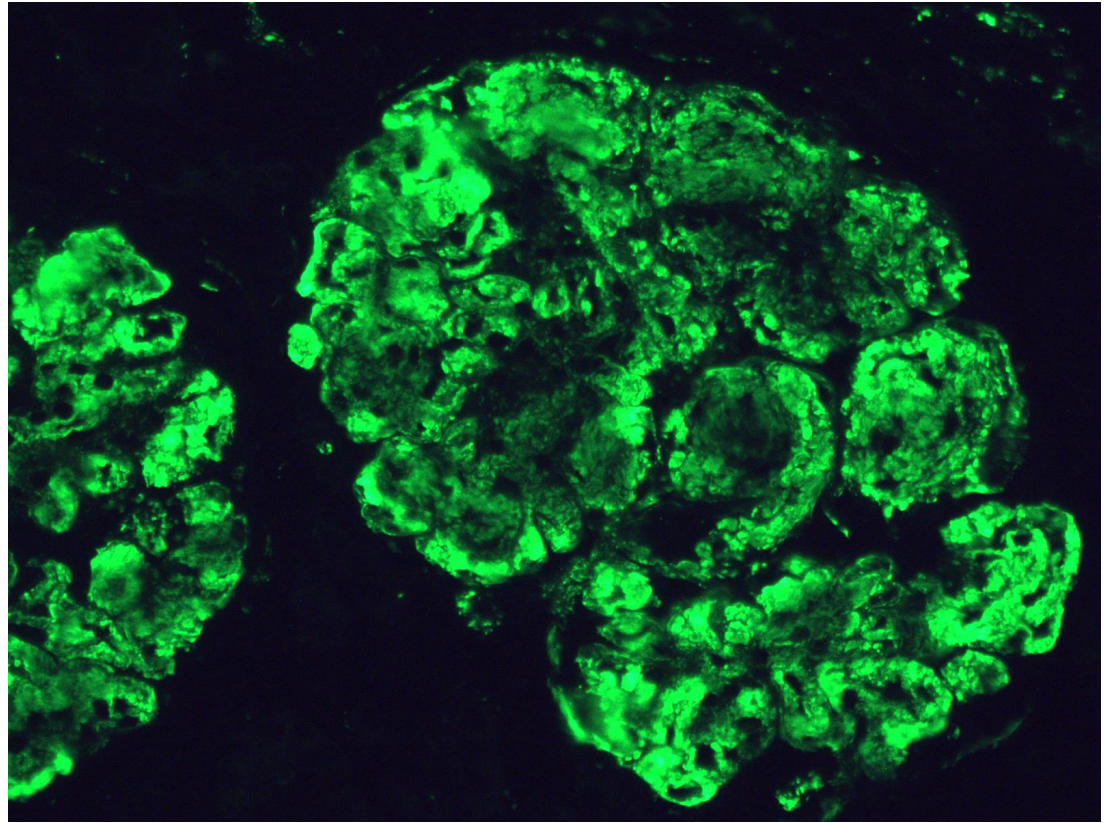


Figure 8.4. Immunofluorescence of C3 glomerulonephritis, MPGN pattern. There is intense staining of mesangial region and along all glomerular capillary walls for C3. (X200). Image courtesy of Dr. Rose Chami.

Management

- Low grade, non-nephrotic range proteinuria and normal creatinine – observation, ACE inhibitor/ARB
- Nephrotic range proteinuria, deteriorating renal function, limited fibrosis on biopsy – steroids + MMF (first line). Consider other options if not responding.

IgA Nephropathy

Clinical Features

- Generally presents in 2nd -3rd decade of life, M>F, higher incidence in white, Asian and Indigenous patients
- Variety of presentations – gross hematuria, asymptomatic microscopic hematuria +/- proteinuria, acute glomerulonephritis, nephrotic syndrome, or a mixed nephritic-nephrotic state
- Most commonly, gross hematuria that is “synpharyngitic”, occurs along with an URTI (1-2 day latency period vs. much longer in post-infectious GN)
- Pathophysiology: an immune-complex mediated GN. Abnormalities in IgA-1 galactosylation leads to antibody deposition in the mesangium which leads to cellular proliferation, proinflammatory cytokines and glomerular injury over time
- Henoch Schonlein Purpura (IgA Vasculitis) and IgA nephropathy are on a spectrum – a renal biopsy of a patient with HSP will look identical to that of a patient with IgA nephropathy.
- HSP is the systemic form with arthritis, purpuric rash and abdominal pain with possible intussusception.

Diagnosis

- Normal complement on GN workup. <20% of patients will have elevated IgA, so they may not be helpful for diagnosis/prognostication.
- May see abnormal renal function, urinalysis and microscopy showing RBCs +/- proteinuria
- Indications for biopsy to make the diagnosis: ongoing proteinuria, hypertension, abnormal creatinine
- Biopsy shows glomerular IgA deposition in the mesangial area on immunofluorescence along with mesangial proliferation, endocapillary hypercellularity, +/- crescents; can also find C3 and IgG/IgM deposition
- Oxford Classification: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C), forms the MEST-C score

Management

- Follow up over time
- Generally for isolated microscopic hematuria or recurrent gross hematuria without proteinuria, no treatment required
- If non-nephrotic range proteinuria, consider supportive anti-proteinuric treatment with ACE-inhibitor/ARB
- Treat hypertension with ACE-inhibitor/ARB
- If nephrotic range proteinuria, worsening renal function, signs of crescentic glomerulonephritis, may need immunosuppression with steroids (sometimes pulse steroids) +/- other immunosuppressive medications (i.e. cyclophosphamide) though the evidence is scarce.
- Important cause of CKD/ESKD – 20-40% of paediatric patients can progress over time, especially with proteinuria/hypertension, biopsy findings of scarring/crescents/tubular atrophy/interstitial fibrosis

IgA Vasculitis (previously Henoch-Schönlein Purpura), a small vessel vasculitis

Clinical Features

- Most common paediatric systemic vasculitis
- 90% of cases are in children <10y old, more common in Caucasian and Asian
- Non-thrombocytopenic purpura predominantly in the lower limbs
- Abdominal pain
- Arthritis or joint pain
- Nephropathy: proteinuria >0.3 g/day or protein:creatinine ratio >30 mg/mmol) or hematuria (>5 RBC/hpf)
- Course is usually mild and self-limited
- 30-50% will have some degree of renal involvement that always occurs after skin lesions appear and are more likely in M>F, age >10 , severe GI involvement, and relapses
- The more severe the renal involvement, the more likely CKD will occur long term

Diagnosis

- Clinical diagnosis: EULAR/PRINTO/PRES criteria: non-thrombocytopenic skin purpura and at least 1 other criteria of those listed above and histopathology showing leukocytoclastic vasculitis with IgA depots or renal biopsy with proliferative GN and IgA deposits
- Biopsy indications
 - If AKI or nephritic syndrome at initial presentation
 - Nephrotic-range proteinuria after 4 weeks or protein:creatinine ratio >100 mg/mmol after 3 months

Management

- KDIGO: RAAS blockade (ACEi or ARB) for 3-6 months in those with persistent proteinuria >0.5-1 g/day/1.73m²
- Steroids and immunosuppressants (mycophenolate, azathioprine) in severe cases

Thin-Basement Membrane Disease/Nephropathy

Clinical Features

- Previously known as benign familial hematuria (term no longer used as there can be risk of progression to CKD)
- Diagnosed in about 1% of population clinically
- Diffuse thinning of glomerular basement membrane
- Patients present clinically with microscopic hematuria (persistent or intermittent), macroscopic hematuria (in the context of URTI)
- Non-nephrotic range proteinuria +/- hypertension (represents a more severe phenotype)
- Generally strong family history of microscopic hematuria without hearing loss/ progression to CKD/ESKD (would be a red flag for Alport!)
- Normal complement, renal function tests

Diagnosis

- Autosomal dominant inheritance, defect in COL4A3 or COL4A4, alpha-3 and alpha-4 chains of collagen type IV which forms part of the glomerular basement membrane (mutations in these genes can also cause Alport syndrome)
- Diagnosis generally assumed by clinical suspicion if family member screening also reveals microscopic hematuria
- Biopsy only performed if concurrent proteinuria, hypertension, increased creatinine or other red flag in order to distinguish between other causes (i.e. Alport syndrome or IgA nephropathy)

Management

- Long-term prognosis is favourable with isolated microscopic hematuria
- FSGS can develop over time in some patients
- Ensure follow up to look for proteinuria, hypertension
- May benefit from ACE inhibitor/ARB if proteinuria present

Alport Syndrome, hereditary type IV collagen disease

Clinical Features

- Can initially present as thin basement membrane disease
- Hematuria: classically intermittent gross episodes on a background of persistent microscopic hematuria
- Proteinuria is a later feature
- Progressive kidney failure (100% ESRD in males with X-linked, usually in adolescence and adulthood)
- Ocular abnormalities
- Lenticonus
- Central or peripheral retinopathy
- Giant macular hole
- Temporal retinal thinning
- Early onset hearing loss

Diagnosis

- 85% are X-linked COL4A5 mutations
- 15% are autosomal recessive with mutations in COL4A3 or COL4A4 on separate chromosomes
- Those with hematuria and any of lamellated GBM, hearing loss or retinopathy should be tested for COL4A3 COL4A4 COL4A5
- Genetic testing more sensitive and specific than renal biopsy
- Renal biopsy can assess damage and concurrent abnormalities

Management

- RAAS blockade (ACE inhibition). Recent guidelines support early initiation of RAAs blockade based on albuminuria and genetics.
- Supportive management for CKD
- Risk of anti-GBM disease (described below) occurring post-transplant in patients with Alport syndrome

Anti-GBM Disease; Goodpasture disease

Clinical Features

- Antibodies directed towards an antigen in the glomerular basement membrane, and alveolar basement membrane. Primary target is alpha-3 chain of type IV collagen.
- Goodpasture disease/syndrome traditionally refers to the combination of glomerulonephritis and pulmonary hemorrhage.
- Bimodal distribution, younger patients more likely to present with pulmonary hemorrhage as opposed to older patients (isolated GN)
- May be triggered by prior infection, immune dysregulation, rarely genetic/familial susceptibility
- Most patients present with rapidly progressive glomerulonephritis (rising creatinine, proteinuria, gross hematuria with active sediment).

- Pulmonary symptoms include shortness of breath, cough, hemoptysis, pulmonary infiltrates on chest X-ray
- Systemic symptoms of malaise, weight loss, fever should raise concern for concurrent vasculitis

Diagnosis

- Demonstration of anti-GBM antibodies in the serum (usually a bit faster turnaround, but need a kidney biopsy to confirm) or kidney biopsy
- Renal biopsy can show a crescentic glomerulonephritis
- Immunofluorescence – linear deposition of IgG along glomerular capillaries and sometimes distal tubules
- Also test for anti-neutrophil cytoplasmic antibodies (ANCA) – usually anti-MPO antibodies because long-term management should be directed towards the vasculitis component
- Chest X-ray, CT is helpful to look at pulmonary involvement

Management

- For rapidly progressive GN and/or pulmonary involvement, plasmapheresis is recommended, along with steroids, cyclophosphamide or Rituximab and MMF
- Supportive care with dialysis, some patients may require ICU for mechanical ventilation
- Continue to monitor clinical status, anti-GBM levels (usually become undetectable after treatment)
- Relapses are rare, unless ANCA positive as well
- Anti-GBM antibodies need to be undetectable prior to transplantation
- Renal prognosis is poor for patients who require dialysis at diagnosis, or those with crescentic GN. Survival approx. 80% based on summary of case reports in literature

Lupus Nephritis

Clinical Features

- SLE: systemic, episodic autoimmune disease with auto-antibodies triggering a wide-spread inflammatory response in connective tissue and vasculature
- Neonatal lupus
- Drug-induced lupus
- F>M in adolescence, in childhood equal F:M
- Non-specific for acute glomerulonephritis: Hematuria (microscopic or gross), proteinuria (+/- nephrotic syndrome), urinary casts (RBC, granular, hyaline), HTN, peripheral edema, acute and/or chronic kidney injury
- Variety of other clinical features can indicate systemic lupus
 - Joint pain +/- arthritis
 - Serositis (hepatitis, pleuritis, carditis)
 - Rash: malar or discoid, photosensitivity
 - Mucous membrane ulceration
 - Fatigue, fever, weight loss
 - Neurologic involvement: seizures, psychosis
 - Cytopenias

Diagnosis

- Kidney biopsy is gold standard
 - Full house immunofluorescence (C1q, C3, IgA, IgG and IgM)
 - Wire Loop deposits
 - Injury classification (ISN/RPS)
 - Note: clinical-pathological correlation is often poor. In other words, can seem mild clinically and have significant histological findings.
- Immunologic workup: ANA, anti-dsDNA, anti-Sm, anti-phospholipid Ab

Management

- Initial therapy:
 - Mycophenolate mofetil or Cyclophosphamide

- High dose steroids with a taper
- Can consider rituximab for non-responsive patients
- Maintenance therapy:
 - Mycophenolate mofetil or azathioprine
 - Steroids
 - ACE inhibitors
 - Hydroxychloroquine for relapse prevention and to manage skin manifestations
 - Avoidance of sun exposure as can trigger relapses

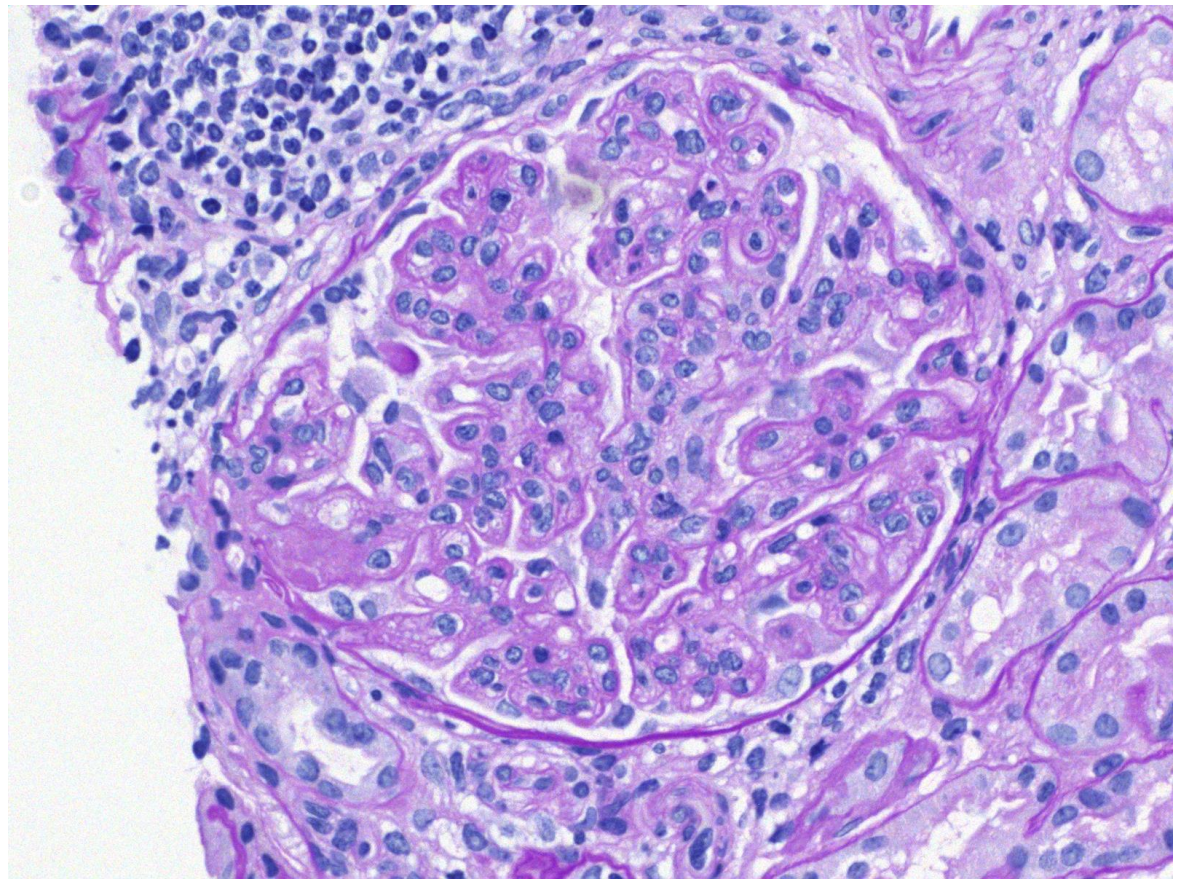


Figure 8.5. Lupus nephritis classes IV and V – mixed, diffuse proliferative and membranous glomerulonephritis. A glomerulus with endocapillary hypercellularity, mesangial hypercellularity, and thickened glomerular capillary walls with double contour formation. (PAS, X200). Image courtesy of Dr. Rose Chami.

ANCA-associated vasculitides

Clinical Features

- Includes granulomatosis with polyangiitis (GPA) – previously known as Wegener's, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (eGPA)– previously known as Churg-Strauss
- GPA is more common than MPA. eGPA is very rare in children
- Kidney involvement is common, and contributes significantly to morbidity and mortality
- Can present with a rapidly progressive glomerulonephritis
- 30%-40% of children progress to CKD by adulthood
- Other clinical features: fever, rash, unexplained monoarthritis, serositis, pulmonary-renal syndrome
- **GPA:** c-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies), specific for PR3 (proteinase 3) are associated with GPA

- Small and medium-sized vessels involved
- EULAR/PRINTO/PRES criteria (3/6): renal involvement (hematuria, proteinuria, RBC casts, necrotizing pauci-immune GN), upper airway involvement (epistaxis, saddle nose, sinusitis etc.), laryngotracheobronchial stenosis, pulmonary involvement, ANCA positivity, granulomatous inflammation within arterial wall or perivascular area on biopsy
- **MPA:** p-ANCA (perinuclear antineutrophil cytoplasmic antibodies), usually directed towards MPO (myeloperoxidase)
 - Small vessels affected, can be a spectrum with GPA
 - Renal involvement predominates – focal segmental glomerulonephritis
 - Can involve pulmonary hemorrhage
- **eGPA:** can have both anti-PR3 and anti-MPO antibodies
 - Small vessels involved
 - Associated with asthma and eosinophilia, not typically renal disease

Diagnosis

- Bloodwork – along with general GN screen, ESR/CRP, thrombotic screen, check for anti-PR3, or anti-MPO antibodies
- Diagnosis is made by renal biopsy (gold-standard), which usually shows a pauci-immune necrotizing glomerulonephritis
- Pauci-immune = immunofluorescence shows few or no immune deposits
- Other tests can include CT/MRI (to assess pulmonary involvement, sinuses, upper respiratory tract)

Management

- Induction: Steroids, Rituximab (over IV cyclophosphamide). Plasma exchange still considered for severe renal or alveolar hemorrhage.
- Maintenance: Rituximab, Azathioprine
- Collaborative management with rheumatology and nephrology

Tubulointerstitial

Acute interstitial nephritis

Clinical Features

- Often associated with medications, but can also be associated with autoimmune disorders/systemic diseases (i.e. SLE, sarcoidosis) and infections (bacterial and viral)
- Common medication causes: penicillin and other antibiotics, NSAIDs, proton pump inhibitors
- Tubulointerstitial nephritis with uveitis: specific syndrome with interstitial nephritis along with uveitis, systemic symptoms (fever, weight loss, fatigue)
- Clinically can present with malaise, vomiting, oliguria, rare gross hematuria, and can even be asymptomatic. Proteinuria less common.
- Classic triad – rash, fever, eosinophilia is more rare

Diagnosis

- Can do urine for eosinophils as a screen, but would be diagnosed via biopsy. Urine sediment can show leukocytes, red blood cells, and white cell casts, but generally no RBC casts
- Biopsy usually performed if considering treatment with steroids
- Biopsy shows interstitial edema and interstitial infiltrate with lymphocytes, monocytes, eosinophils

Management

- Discontinuation of the likely causative agent
- Consider steroids for patients with severe AKI

Acute tubular necrosis (ATN)

- See section on acute kidney injury for further details regarding ATN

Vascular

Renal Vein Thrombosis

Clinical Features

- Gross hematuria, thrombocytopenia, flank mass, hypertension
- General risk factors: dehydration, shock, prothrombotic state (e.g. genetic prothrombotic mutations, nephrotic syndrome, post-transplant)
- Neonates can also present with RVT. Risk factors in neonates include: infant of diabetic mother, polycythemia, prematurity, perinatal asphyxia, umbilical lines

Diagnosis

- Ultrasound with doppler (may show swollen kidney). Check for extension into IVC. May need further CT angiogram if high suspicion. Full coagulation workup.

Management

- In consultation with hematology, conservative management or anticoagulation with low molecular weight heparin. If severe bilateral RVT may require fibrinolytic therapy.
- Long-term outcomes can include atrophy of the kidney, CKD, hypertension and proteinuria.

Renal Artery Thrombosis (rare)

- Acute onset of flank pain, fever, nausea, hypertension, AKI, gross hematuria

Nutcracker syndrome (rare)

Clinical Features

- Compression of the left renal vein between the superior mesenteric artery and aorta. Can lead to flank pain, intermittent gross hematuria, intermittent proteinuria

Diagnosis

- Ultrasound with doppler, may need further CT angiogram/venogram if high suspicion

Management

- In consultation with urology/surgery

LOWER URINARY TRACT & SYSTEMIC CAUSES

- Infection – Bacterial, viral cystitis, Yeast, Parasites
- Trauma (surgery, catheterization, motor vehicle accident)
- Calculi
 - *Note: consider idiopathic hypercalcuria as cause of persistent microscopic hematuria
- Tumour (Wilm's tumour, nephroblastoma)
- Coagulopathy

Making the Diagnosis

- Urine culture
- Imaging – renal and bladder ultrasound, +/- Plain film (for stones), +/- CT Abdomen/Pelvis (for trauma or high suspicion for stones)
- Urine calcium:creatinine ratio, +/- further urine spot ratios of oxalate, urate, citrate to creatinine, +/- 24 hour urine collection for stone workup
- INR/PTT, CBC (check platelets), further coagulation screen as indicated

Management and follow up

- See Chapters on Urolithiasis, Urinary Tract Infections

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3

SECTION 3

Management of Acute and Chronic Kidney Disease in Paediatric Nephrology

OUTLINE

- 9. Chronic Kidney Disease
- 10. Renal Replacement Therapy
- 11. Basics of Kidney Transplantation
- 12. Thrombotic Microangiopathy

Abbreviations

GN = glomerulonephritis
INR = international normalized ratio
IUGR = intrauterine growth restriction
IV = intravenous
IVIG = intravenous immunoglobulin
KDIGO = kidney disease improving global outcome
KDOQI = kidney disease outcomes quality initiative
K = potassium
Kg = kilogram
LDH = lactate dehydrogenase
LDL = low density lipoprotein
LVH = left ventricular hypertrophy
MBD = metabolic bone disease
Mcg = micrograms
Mg = miligram
mL = mililitres
MMF = mycophenolate mofetil
MMR = measles, mumps, rubella
MPGN = membranoproliferative glomerulonephritis
Na = sodium
NDD = neurological determination of death
NKF = national kidney foundation
NODAT = new onset diabetes after transplant
OGTT = oral glucose tolerance test
PAP = papanicolaou test
PD = peritoneal dialysis
PO = per mouth
PO₄ or Pi = phosphate

PPI = proton pump inhibitor
PRA = panel reactive antibody
PCR = protein to creatinine ratio
PTH = parathyroid hormone
PTLD = post-transplant lymphoproliferative disorder
PTT = partial thromboplastin time
QOL = quality of life
R&M = routine and microscopy
RBC = red blood cell
rHuEPO = Recombinant Human Erythropoietin
RODS = renal osteodystrophy scan
RRT = renal replacement therapy
SCT = stem cell treatment
SLE = systemic lupus erythematosus
SPF = sun protection factor
STEC = shiga-toxin E-Coli
TLS = tumor lysis syndrome
TMA = thrombotic microangiopathic anemia
TPE = therapeutic plasma exchange
TSAT = transferrin saturation
TST = tuberculin skin test
TTP = thrombotic thrombocytopenia purpura
UF = ultrafiltration
URTI = upper respiratory tract infection
UTI = urinary tract infection
UV = ultraviolet
VEGF = vascular endothelial growth factor
VZV = varicella zoster virus
WBC = white blood cell

9. CHRONIC KIDNEY DISEASE

OVERVIEW

- Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, when there are irreversible bilateral abnormalities of the renal parenchyma.
- CKD is classified based on cause and GFR category.
- True incidence of CKD in childhood is unknown as many children remain undiagnosed or do not present until adulthood.

Causes of CKD in Children

- CAKUT (congenital anomalies of the kidney and urinary tract), reflux nephropathy
- Inherited disorders (Ciliopathies, familial nephropathies)
- Glomerular causes (GN, vasculitides, nephrotic/focal segmental glomerulosclerosis, aHUS, SLE)
- Renal stone diseases
- Secondary to AKI
- HUS/TMA

Table 9.1 Staging of CKD

Stage	GFR (mL/min/1.73m ²)	Features
1	≥90	Usually no symptoms, renal parenchymal disease present
2	60-89	Usually no symptoms, at lower GFR range may develop biochemical imbalances
3	30-59	Biochemical abnormalities present, anemia. May have poor growth
4	15-29	More severe symptoms
5	<15	Renal replacement therapy/and or transplantation required

- GFR can be estimated using the equation known as the modified Schwartz formula:

$$\text{GFR (ml / min/ 1.73m}^2\text{)} = K * \text{Ht (cm) / Pcr (}\mu\text{mol/L)}$$

- Where K is a constant determined by regression analysis for different ages (K= 36.5)
- Ht = height in cm
- Pcr = plasma creatinine in $\mu\text{mol/L}$
- This equation is valid only for children 2-16 years of age with eGFR <90 mL/min/1.73 m²
- It can also be estimated using the CKID equation (https://www.kidney.org/professionals/kdoqi/gfr_calculatorped)

Considerations for Infants & Young Children

- The criteria of duration of >3 months does not apply to infants less than 3 months of age
- Infants may have normal serum creatinine but will still meet criteria for definition of CKD based on structural abnormalities
- Normal GFR in newborns is as low as 30-40 ml/min/1.73m², doubles by 2-4 months of age and only reaches adult levels by 2 years of age
- GFR threshold values for CKD apply to children only >2 years. Therefore, children under 2 years of age should be categorized as having normal, moderately reduced, or severely reduced age-adjusted GFR
- eGFR equations are not validated below the age of 1

MAKING THE DIAGNOSIS

Presentation of CKD

- Many present in the newborn period, following antenatal diagnosis (note some are missed depending on prenatal scans/care or lack thereof)
- Urinary tract infections
- Polydipsia, polyuria
- Family history of CKD
- Short stature

- Poor appetite/failure to thrive
- Anemia
- Lethargy
- Nausea
- Proteinuria
- Hypertension
- Bony abnormalities from renal osteodystrophy
- May have no obvious symptoms

History & Physical Examination (see *Chapter 1 for details*)

- Antenatal/birth history (gestational age, amniotic fluid level, antenatal US, maternal drug history, maternal diabetes)
- Birth weight (any IUGR?), type of delivery, any use of umbilical catheters
- Consanguinity?
- How is the urinary stream? (concern for obstructive uropathy)
- Symptoms of CKD (as outlined above)
- Height, weight, BP
- General physical examination, including looking for signs of dysmorphic features
- Pubertal stage

Investigations/Work-Up

- Obtain urine for microscopy, protein/creatinine ratio
- Imaging (ultrasound most common)
- Labs
 - CBC for anemia
 - Electrolytes (include calcium, phosphate, magnesium)
 - Creatinine, Urea
 - PTH
 - Other relevant ones to aid diagnosis

MANAGEMENT & FOLLOW UP

OVERARCHING GOALS

- Early identification of etiology and timely intervention can improve prognosis and limit disease progression
- Slow progression
 - control proteinuria
 - manage BP
- Promote normal growth and development
- Maintain normal biochemical and acid-base balance
- Manage anemia
- Manage bone health

A. CKD AND DEVELOPMENT/CNS ISSUES

Overview

- CKD is a chronic illness, with the potential to disrupt the development and learning throughout childhood and adolescence
- Factors impacting neurodevelopmental function include:
 - Nature of renal disease and treatment intensity
 - Age of onset of the disease (approximately 40% of paediatric CKD is present from birth)
 - Genetic causes of renal disease that may also affect neurodevelopment
 - Insults to the developing brain such as uremia, hypertension, etc.
 - Missed opportunities for schooling
 - Social and emotional experiences due to nature of illness/treatments/lack of opportunity for independence from family unit

Making the Diagnosis

- Assessment of developmental milestones

- Be aware of burden of disease for paediatric CKD patients
- Allow opportunity to discuss and bring concerns regarding academics and age appropriate social/emotional interactions
- Make the diagnosis: psychology/developmental specialists

Management/Follow-Up

- Ensure that the appropriate supports are in place (primary care specialist and/or developmental specialist)
- Advocate for accommodations/interventions be made for the child where required
- Support the family: social work/child life specialists
- Have an organized transition from paediatric to adult CKD program, where the goal early on is for the child to have the ability to be responsible for their own healthcare decisions (medications, treatments, and quality of life)

B. HYPERTENSION IN CKD

Overview

- Actively contributes to progression of CKD
- Is a complication of CKD
- Children with CKD most often have secondary HTN with intrinsic renal parenchymal disease and renovascular disease being the most common causes
- Pathophysiology of hypertension and progression of CKD

1) HTN

- Abnormal vascular regulation
- +/- fluid overload
- ↑cardiac output
- Increased peripheral vascular resistance
- RAAS activation due to angiotensin II-mediated vasoconstriction, salt and water retention, and sympathetic hyperactivity

2) Loss of nephron mass causes glomerular hyperfiltration

3) Proteinuria

- Result of damage in glomerular capillary wall or by decrease in tubular reabsorption = cause increased damage to renal tubular cells
- Hypertension prevalence is estimated to be about 50% in paediatric patients with CKD
 - Increased BP correlates to CKD progression (eGFR decreases, BP ↑)
 - HTN in CKD is a risk factor for accelerated deterioration of kidney function and cardiovascular disease
- Masked hypertension (normal clinic BP but elevated ambulatory BP) in CKD is associated with end organ damage such as LVH

Making the Diagnosis

- Measure BP at every clinic visit manually using proper technique (right arm)
 - Use average of BP readings
 - Use BP percentile tables for age/sex/height
 - Validated for manual BP, not oscillometry
- Gold standard is ABPM (ambulatory blood pressure monitoring)
 - KDIGO recommends yearly ABPM (regardless of clinic BP to assess for masked HTN) and monitoring of BP manually (every 3-6 months)
 - ABPM not appropriate for young children (<6 years of age) related to lack of normative data and difficulty in completing the test
- At every clinic visit check urine for protein/creatinine ratio
 - Consider first morning urine to rule out orthostatic proteinuria for adolescents

Management/Follow-Up

- First line therapy ACE-I or ARB for HTN (with or without proteinuria) unless medically contraindicated (such as hyperkalemia, risk of AKI, or concerns of reduction of residual urine output in advanced stages of CKD, adverse fetal risks for pregnant women, etc.)
 - BP treated to lower 24hr MAP by ABPM to less than or equal to 50th percentile for age/sex/height
- Where ABPM results not available BP treatment target <90th percentile for age/sex/height (manual readings)

- At lower GFR, may need to consider alternative agents to ACE-I/ARB. See hypertension section for other treatment options.
- Echocardiogram for CKD patient with any HTN to assess for end organ damage (LVH) and repeated 6-12 month intervals to assess for improvement/progression
- Yearly ABPM for CKD patients or every 6 months based on the clinical condition
- Lifestyle
 - Reduced salt diet
 - Fluid target (need to prevent AKI, may require fluid restriction in advance stages of CKD)
 - Promote physical activity and healthy lifestyle

C. CKD AND GROWTH/NUTRITION

Overview

- Achieving normal growth is challenging in CKD
- Approximately 40% children with ESRD have significantly reduced height compared to controls
- Cause of impaired growth is multifactorial and can include IUGR, malnutrition, metabolic acidosis, anemia, mineral and bone disease, medications (steroids), growth hormone insensitivity, functional deficiency of insulin-like growth factor (IGF1), underlying cause of CKD (e.g. cystinosis)
- Infants with CKD are challenging to maintain on adequate nutrition due to frequent vomiting/reflux/anorexia

Making the Diagnosis

- Monitor growth (length and weight) and plot on growth chart at each visit
- Complete dietary assessment to evaluate calorie and protein intake
- Bicarbonate, PTH, CBC (assess for anemia), electrolytes and thyroid function tests
- If considering initiating GH therapy (see below), calculate mid-parental height, do bone age x-ray (left wrist) and fundoscopic exam at baseline prior to starting therapy, assess pubertal status according to Tanner staging

Management

- If poor caloric intake and having poor growth start on dietary supplementation (orally or by nasogastric tube or gastrostomy)
 - Many children/infants with CKD require gastrostomy tube to help with adequate nutritional intake
- Correct any acidosis, hyperparathyroidism or thyroid derangements
- Consider PPI and domperidone for infants with severe vomiting affecting nutritional intake
- Consider appetite stimulant if poor appetite contributing to poor caloric intake
- Despite adjusting for all these CKD associated growth limiting factors and growth still poor-- consider starting GH therapy
- Criteria for GH eligibility (refer to the guidelines on the CAPN website) <https://www.capneph.ca/physicians/cpg-growth-hormone-guidelines.html>
 - CKD stages 2 to 5
 - Bone age: epiphyses not fused
 - Height and height velocity
 - Height SDS ≤ 1.88 (3rd percentile) or Δ Height SDS < 0 when height < 10 th percentile or Height > 2 SD below the mid-parental height.

Follow-Up

- Monitor growth
- After first year on GH if height velocity < 2 cm/yr assess compliance, dose and nutritional factors
- GH dose 0.045mg/kg/day-0.05mg/kg/day by subcutaneous injection
- Dose adjustment of GH to body weight on regular intervals
- Hold dose in the case of uncontrolled severe secondary PTH, intracranial HTN , active neoplasm, or progressive scoliosis (discuss with orthopedics)
- Stop GH when height velocity drops to less than 2 cm/year and/or epiphyseal plate closure, patient reaches genetic target height percentile, patient receives transplant, patient or parent request, non-adherence, malignancy

D. CKD AND ANEMIA

Overview

- Multifactorial etiology, principal etiology is reduced erythropoietin (EPO) by the kidneys
- As GFR decreases, EPO deficiency worsens (usually begins when eGFR 35 ml/min/1.73^{m2} or less)
- Additional causes--iron deficiency, blood loss, malnutrition, high PTH, medications (ACE-I), hemolysis, B12 or folate deficiency, systemic diseases (inflammation), red cell disorders (hemoglobinopathy), etc.
- Iron deficiency, serum transferrin saturation < 20% independent predictor of anemia
- Ferritin not a good marker for iron deficiency in CKD as ferritin increased in patients with concurrent inflammation
- May develop iron deficiency after initiating ESA due to depletion of iron stores
- Clinical effects of anemia include decreased quality of life, fatigue, LVH, loss of appetite etc.

Making the Diagnosis

- The diagnosis of anemia in children with CKD should be based on age and gender specific normal ranges.
- Initial evaluation: CBC, reticulocyte count, ferritin, iron, total iron binding capacity, and TSAT (<20%)
- Normocytic anemia with relative reticulocytopenia is consistent with EPO deficiency, macrocytosis or microcytosis present then consider alternate etiologies

Management/Follow-Up

- Routine monitoring of CBC and iron stores in children with CKD (varies depending on the child and whether they are stable on ESA with target hemoglobin, or initiating/adjusting dose of ESA)
- Consideration of IV iron if not responsive to oral iron
- Blood transfusions should be reserved for children who are unresponsive to ESAs or symptomatic anemia as can sensitize a patient for future transplantation
- KDIGO recommends targeting paediatric CKD patients hemoglobin levels between 110-120 (130 in some centres)

- Upper limit is not known but adult studies have shown increase in cardiovascular events with higher hemoglobin levels and excessively high doses of ESA
- Erythropoiesis stimulating agents (ESA) help to increase hemoglobin levels
- All patients starting an ESA should also receive iron supplementation except when iron overload is present
- Recombinant Human Erythropoietin (rHuEPO) or Darbepoetin α
 - Subcutaneous or IV
 - Wide range of dosing requirements based on age, CKD stage, mode of dialysis, route of administration
 - rHuEPO shorter acting, Darbepoetin longer acting
 - Site of injection should be rotated
 - Frequent dose adjustments are common
 - Complications--may see increase in BP after starting rHuEPO, rare complication anti-EPO antibodies

E. CHRONIC KIDNEY DISEASE-BONE MINERAL DISORDER

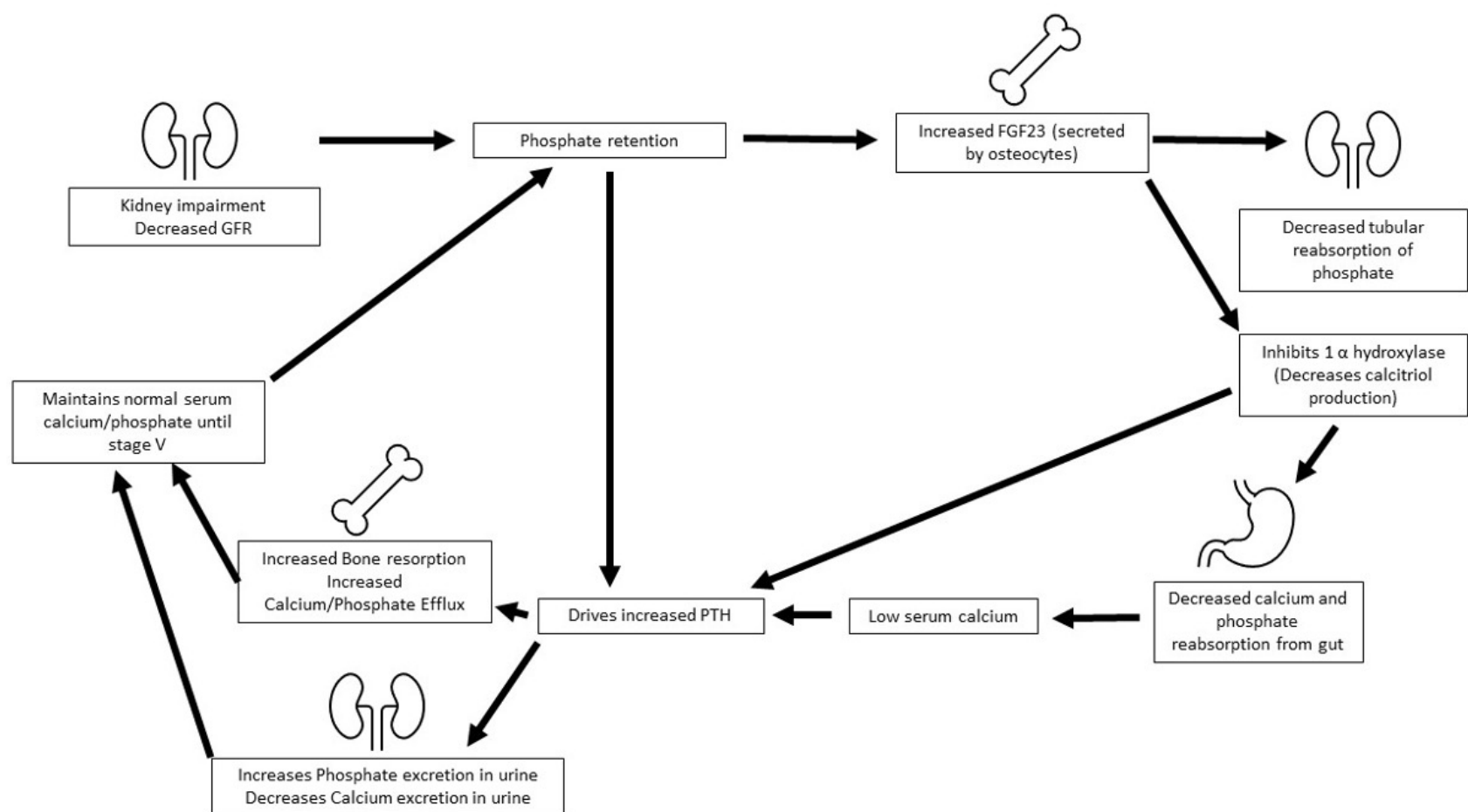


Figure 9.1. Pathogenesis of CKD-MBD (described in words below).

Pathogenesis of CKD-MBD

The onset of the CKD-MBD happens in very early CKD.

- Kidney disease → decrease bone formation + high inorganic phosphate (Pi) → stimulate osteocytes to secrete fibroblast growth factor-23 (FGF-23) → decreases tubular reabsorption of (Pi) + inhibits 1-alpha hydroxylase → decrease calcitriol production
- Low calcitriol → decreases calcium (Ca) and phosphate (PO₄) absorption from the gut
- Low Ca → Stimulates parathyroid hormone (PTH) → increases bone turnover and releases more Ca and PO₄ from bones. PTH also acts on the kidneys to reabsorb Ca and secrete PO₄ in urine.
- This serves to keep Ca/PO₄ levels in normal range until later stages of CKD when the response will be inadequate.

Definition

The definition of CKD-MBD in children is manifested by one or a combination of the following three components with CKD stages 2 through 4:

- Abnormalities of Ca, PO₄, PTH, FGF23, and vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength
- Extra skeletal calcification

Clinical Manifestations

- Similar to those with vitamin D deficiency
- Fractures
- Deformities e.g. valgus and varus deformities
- See Figure 9.2

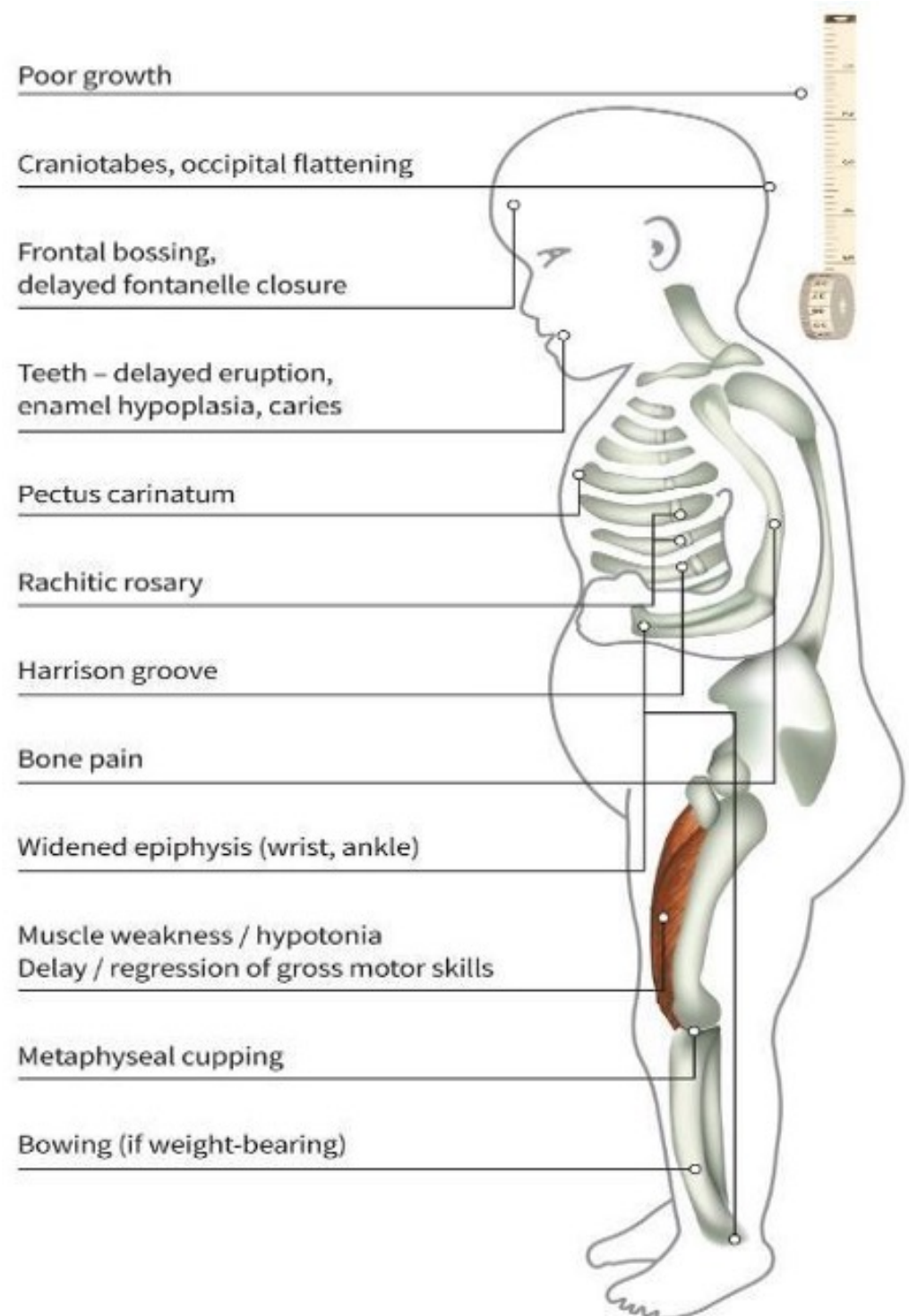


Figure 9.2. Physical manifestations of Rickets

Figure used with permission from Prasad C, Cummings E.

Rickets presenting as gross motor delay in twin girls. CMAJ. 2018 05 7;190(18):E565-E568.

Laboratory Findings

- High phosphate levels: results in 1,25-dihydroxyvitamin D deficiency, hypocalcemia, and secondary hyperparathyroidism.
- Low 1-25 dihydroxy vitamin D levels (not measured routinely)
- Serum calcium abnormalities: usually hypocalcemia; however, they can have hypercalcemia from therapeutic interventions or tertiary hyperparathyroidism
- High PTH levels
- High alkaline phosphatase (ALP) levels

Screening and Monitoring

Patients with CKD-MBD should be screened and monitored for the following. The frequency of monitoring depends on the stage of CKD:

- Calcium
- Phosphate
- PTH
- ALP
- 25-hydroxyvitamin D
- Some centres also monitor for Renal Osteodystrophy using serial X-rays

Complications

- Growth failure
- Rickets
- Fractures: risk is increased 2-3 fold compared to general paediatric population
- Slipped epiphysis and genu valgum
- Extra skeletal calcifications: vascular, ocular, periarticular and visceral
- Renal osteodystrophy: bone biopsy is the gold standard for diagnosis, but typically only done for research purposes

Management & Follow-Up

- Prevent and treat secondary hyperparathyroidism, which results in bone disease
- Allow normal growth and prevent cardiovascular disease and soft tissue calcifications,

- Avoiding aggressive therapy, which can lead to adynamic bone disease.
- While PTH targets vary in different guidelines, overall the approach is to maintain PTH in 2-3x upper limit of normal in patients on dialysis, and a near normal PTH in stages 2 to 4.
- If PTH is progressively rising or persistently above the upper limit of normal, any modifiable factors should be addressed.

Step 1: Control hyperphosphatemia:

- Dietary phosphorus restriction (e.g. dairy, cereals, processed food ..etc.)
- Phosphate binders with meals to bind phosphate and reduce gut absorption. Can be calcium based (i.e. Calcium carbonate), or non-calcium based (i.e. Sevelamer).

Step 2: Treat Vitamin D deficiency if present:

- Ergocalciferol or cholecalciferol (25-OH Vitamin D)

Step 3: Consider active vitamin D:

- Calcitriol/alfacalcidol (1,25-OH Vitamin D): if PTH remains high
- Note that calcitriol increases both Ca and PO₄ reabsorption from gut, thus, phosphate should be controlled first.

Step 4: if PTH remains high, complete workup for tertiary hyperparathyroidism

- Parathyroid ultrasound to rule out parathyroid adenoma
- Consider calcimimetics (i.e. cinacalcet), which increase the sensitivity of Ca-sensing receptor in the parathyroid gland
- Consider parathyroidectomy

Step 5: Calcium:

- Hypocalcemia:
 - IV Calcium if symptomatic
 - Slow infusion with peripheral IV to prevent burns and skin necrosis.
 - Oral Ca supplementation (must be given without food for absorption of calcium)
- Hypercalcemia:
 - Hold calcium-based phosphate binders, calcium supplementation and vitamin D
 - Consider non-calcium-based phosphate binders.

F. ELECTROLYTE ABNORMALITIES AND ACID-BASE DISORDERS IN CKD

Please see Chapter 4 for details of how to identify and manage electrolyte disorders, and acid-base disorders, including dysnatremias.

A few considerations:

- In CKD, electrolyte disturbances in sodium are usually caused by hypervolemia (excess free water retention leading to hyponatremia), or hypovolemia (volume loss with salt wasting secondary to renal dysplasia, also leading to hyponatremia).
- Treatment will include either fluid restriction in the case of hypervolemia, or sodium supplementation in salt-wasting states.
- Hyperkalemia:
 - Can occur when GFR is <10% normal.
 - Caused by low caloric intake, high dietary K intake, acidosis, and anti-hypertensive medications e.g. captopril and spironolactone.
 - Management: Low K diet/formulas – Treat acidosis – K-Binding resins (kayexalate) – Furosemide (watch blood volume to prevent deteriorating renal function in severe CKD)
 - May be an indication to start dialysis depending on GFR
- Metabolic Acidosis:
 - Caused by urinary bicarbonate losses and inability to acidify urine.
 - Leads to growth impairment by utilizing the bone buffering system
 - Management: Maintain $\text{HCO}_3^- > 22$ – use sodium bicarbonate or citrate

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10. RENAL REPLACEMENT THERAPY

OVERVIEW

Renal replacement therapy (RRT), also known as kidney replacement therapy (KRT) is used to supplement the declining kidney function in acute or chronic kidney failure. RRT allows for removal of solutes (uremic waste, ingested toxins and maintenance of acid-base homeostasis and electrolyte balance) and fluid. This can be achieved either with intermittent modalities (Peritoneal dialysis - PD, Hemodialysis - HD, Hemodiafiltration - HDF) or continuous renal replacement therapy (CRRT).

Principles of solute removal

- Diffusion = Movement of solute from an area of high concentration to an area of low concentration through a semi-permeable membrane (Hemodialysis, Peritoneal dialysis)
- Convection = Removal of solute in a stream of solvent (Hemofiltration)

Principles of fluid removal

- Ultrafiltration (UF) = bulk movement of water along with permeable solutes

Table 10.1 Indications for RRT

Short Term	Long Term
• Refractory electrolyte disorder, eg. hyperkalemia and hyperphosphatemia • Refractory acid-base disorder, eg. acidosis • HTN or congestive heart failure secondary to fluid overload • Uremia, especially severe uremic pericarditis and uremic encephalopathy • Toxins, poisons • Inborn errors of metabolism	• Considered when at least GFR <15 mL/min/1.73 m² (different centres have different thresholds for starting RRT) • Fluid overload • Symptomatic uremia (nausea, anorexia, lethargy) • Malnutrition and growth failure • Uncontrolled acid-base or electrolyte disorders

MODALITIES

We decide modality based on several factors including the patient's age, hemodynamic stability (CRRT often favored in unstable patients) the indication (fluid removal versus intoxication), contraindications (e.g., abdominal wall defect precludes PD), presumed duration on dialysis, institutional, parental preference.

1. Peritoneal Dialysis (PD)

- A catheter is placed in the peritoneal space and the peritoneum is used as semi-permeable membrane.
- Frequency: PD is done on a daily basis.
- Principles: Diffusion across the peritoneal membrane results in solute clearance and water removal (=UF) is achieved mainly through osmotic pressure (high glucose concentration in PD solution). Secondary to water removal, some solvents are “dragged” along a pressure gradient, representing convective transport of solutes (mainly for middle molecular weight proteins e.g. urea).
- Prescription includes: # cycles, duration of cycle, daytime dwell, fill volume, dialysis bath
- Types of PD in children:
 - Automated PD (APD): most commonly used, treatment only overnight using a cycler, with/without daytime dwell
 - Manual IPD: intermittent PD, exchanges made manually
 - Continuous Ambulatory PD (CAPD): dialysis solution in peritoneal cavity 24/7, with 3-5 manual exchanges per day

2. Hemodialysis (HD)

- Blood is pumped from the vascular access to the dialyzer and then re-circulated to the patient. Dialysis fluid runs in a countercurrent direction through the dialyzer separated from the blood by a semi-permeable membrane.
- Frequency: HD is often performed as frequently as daily in the acute setting and then generally three days per week over 3-4 hours in chronic HD patients. Home nocturnal dialysis is done every night.
- Principles:

- In HD alone, solute clearance is mainly achieved by diffusion (solute moves from area of high concentration to area of low concentration).
- In hemofiltration (HF, no dialysate is used) there is mass transport secondary to a pressure gradient, which results in solute clearance (convection). In HDF both principles are present. Convection is better for removing mid-sized or larger particles, whereas diffusion is best for small solutes. Therefore, patients established on HD can be switched to HDF to allow for diffusion as well as better clearance of mid-sized solutes using convection.
- Prescription: duration & frequency, blood flow, dialysis flow, urea clearance, dialyzer, dialysate bath and electrolyte content, anticoagulation
- Types: HD or HDF

3. Continuous Renal Replacement Therapy (CRRT)

- Continuous removal of solutes and modification of the volume and composition of extracellular fluid.
- Principles: The patients' blood runs continuously through a filter, using convection +/- diffusion for clearance and allows for slow fluid removal.
- Some filters also have immune-adsorptive function.
- Prescription: dialyzer, blood flow, dialysate flow, replacement fluid, anticoagulation, dialysate bath
- Types: continuous veno-venous hemodialysis - CVVHD, continuous veno-venous hemodiafiltration - CVVHDF, continuous veno-venous hemofiltration - CVVH

Table 10.2 Comparison of Modalities

	PD	HD	CRRT
Advantages	- Easy access and technically simple - Continuous and gradual UF and solute clearance - No need for vascular access, anticoagulation - Readily available throughout the world - Taught to families to be done at home - Better for smaller patients as no need to account for extracorporeal blood volume	- Rapid ultrafiltration and solute clearance (increased compared to PD) - Dialysis done by RNs and not family	- Continuous UF and solute clearance → better to tolerate even if hemodynamically unstable - Combine with ECMO - Increased solute removal compared to PD - Preferred when rebound is expected (e.g. tumour lysis syndrome, rhabdomyolysis, inborn errors of metabolism, etc.)
Disadvantages	- Can cause respiratory distress from abdominal distension - Possible inefficient removal of solutes and fluid - Risk for peritonitis	- Requires blood prime in small patient - Need for vascular access (tunneled central line preferred) - Anticoagulation (relative, can be done without) - Relatively high cost and experienced centre - Risk for infection from access	- Requires blood prime in small patient - Need for vascular access - Anticoagulation (relative, can be done without) - Relatively high cost and experienced ICU needed
Contraindications	- Omphalocele, gastroschisis, diaphragmatic hernia, bladder exstrophy - Intraabdominal infection (relative) - Recent abdominal surgery (relative)	- High risk for anticoagulation (relative as can be done without) - Patient with hemodynamic instability - No vascular access possible	- No vascular access possible

Some Examples	- Small infants - Inability to establish vascular access - Short term use only (e.g. STEC HUS) - No access to HD centre - Better compatibility with lifestyle (e.g. school)	- Inborn error of metabolism* - Toxins, poisoning* - Inability of parents to do PD at home	- Critically ill patient or hemodynamically unstable - Patient connected to ECMO - Inborn error of metabolism - Toxins, poisoning - Tumor lysis syndrome
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*HD/CRRT preferred, but PD can also be used if HD/CRRT not available

Table 10.3 Complications

PD	HD	CRRT
- Peritonitis - Exit site or tunnel infections - Catheter malfunction: In-flow or outflow obstruction - Inadequate UF and clearance - Hyperglycemia - Leak at exit site - Leaks (Hydrothorax, pericardial effusion) - Hernia - Caregiver burnout	- Dialysis disequilibrium syndrome - Vascular access or catheter complications, eg infection, thrombosis, displacement - Clotting of extracorporeal circuit - Hemorrhage - Electrolyte disturbances - Intradialytic hypotension - Intradialytic hypertension - Allergic reactions to blood or dialyzer - Air embolism and microbubbles - Cardiovascular disease including LVH, atherosclerosis, sudden cardiac death - Sleep disorders - Dialysis related amyloidosis	- Vascular access or catheter complications, eg infection, thrombosis, displacement - Hypotension after connection - Hemorrhage - Clotting of extracorporeal circuit - Electrolyte disturbances - Allergic reactions to blood or dialyzer - Air embolism and microbubbles

APHERESIS

In apheresis whole blood from the patient is removed and the apparatus separates blood into its individual components so that a constituent part (RBCs or WBCs), or the plasma

itself is removed (and therefore some pathological circulating factor such as an antibody). Blood is then reconstituted with human albumin solution or fresh frozen plasma and returned to the patient's circulation.

Types of apheresis

- *Therapeutic plasma exchange*: separates out patients' plasma, which is removed and replaced with albumin or plasma (Thrombotic thrombocytopenic purpura, neuroinflammatory diseases, atypical HUS)
- *Leukocytapheresis*: separates out patients' WBCs (e.g. blasts), removes them and returns remainder of blood +/- replacement fluid (hyperleukocytosis)
- *LDL apheresis*: selective removal of low-density lipoproteins and returns remainder of blood (familial hypercholesterolemia)
- *RBC exchange*: separates out red blood cells, removes them and replaces them with pRBCs (sickle cell disease with stroke)

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11. BASICS OF KIDNEY TRANSPLANTATION

OVERVIEW

- Compared with hemodialysis or peritoneal dialysis, kidney transplant is associated with better long-term survival, improved quality of life and improved growth
- 40-50 paediatric kidney transplants each year across Canada
- Causes of kidney disease in children who progress to need a kidney transplant
 - CAKUT (including renal dysplasia, obstructive uropathy) – 31%
 - Genetic causes (e.g. ciliopathies, cystinosis, hyperoxaluria) – 16%
 - Focal segmental glomerulosclerosis (FSGS) – 12%
 - Other glomerulonephritis – 11%
 - Hemolytic-uremic syndrome (HUS) – 3%
 - Other causes (e.g. vasculitis, reflux nephropathy, etc.)
- Donor selection
 - Living donor (related or unrelated) – best outcomes
 - Deceased donor (NDD – after neurological death, DCD – after cardiac death)
 - Exceptional distribution status – legal requirement to advise recipient if donor has certain risk factors (e.g. infection, malignancy, other disease)
- Transplant allocation
 - Administered on a provincial level with slight differences between provinces
 - Generally, priority is given for medical urgency, highly-sensitized recipients, combined organ transplant, and children
 - Children are prioritized in Canada (= shorter wait times)
 - Kidney paired donation program (in Canada) – used to match donor-recipient pairs that are incompatible for any reason
- Graft survival
 - Significantly improved over the past three decades

- Overall, 5 year graft survival ~ 80%, 10 year graft survival ~ 60%

PRE-KIDNEY TRANSPLANT WORK-UP

- Timing of transplant
 - Pre-emptive kidney transplant (avoiding need for dialysis)
 - Preferred strategy, wherever possible
 - Preparations for transplant should start when eGFR decreases to $< 15\text{-}30\text{mL/min/1.73 m}^2$ (at least 6-12 months before anticipated need)
 - If already on dialysis
 - Referred when ESKD deemed irreversible, medically stable and underlying disease adequately controlled
- Transplant contraindications
 - Active malignancy, sepsis/active infections
 - Multi-organ failure, severe cardiac or pulmonary disease, other life-limiting or progressive disease
 - Active kidney disease (e.g. vasculitis, HUS, etc) – in remission for at least 6 months
 - Significant non-adherence concern
- Pre-transplant considerations
 - Urological issues – may need to correct significant abnormalities
 - Small bladder capacity (if patient is anuric)
 - Abnormal bladder function
 - Urinary tract obstruction
 - Recurrent UTI with redundant/dilated native collecting system
 - Nephrectomy of native kidneys
 - Potential indications
 - Severe refractory hypertension
 - Polycystic kidneys – inadequate room for graft due to native kidney volume
 - Recurrent / chronic pyelonephritis
 - High-grade proteinuria

- High risk of kidney malignancy (e.g. Denys-Drash syndrome)
- Significant polyuria
- Immunizations
 - Strongly recommended to have completed all routine childhood immunizations prior to transplant (accelerated schedules exist)
 - Additional vaccines needed:
 - Hepatitis A
 - 4CMen-B
 - Pneu-P-23
 - Influenza
 - HPV
 - Yellow fever (optional, if planning future travel)
 - Refer to Canadian Society of Transplantation 2020 immunization consensus statement for further information

Table 11.1. Suggested pre-kidney transplantation lab work-up*

Typical CKD follow up labs + the following:

AST, ALT, ALP, GGT, bili, amylase/lipase, total protein, albumin
HbA1c and glucose
Lipid profile
Additional labs depending on the primary disease
Coagulation Studies: PTT, INR
Additional coagulation studies may be needed
CRP, IgG, IgM, IgA
24 hour urine – for volume, creatinine and protein
Type & Screen
HLA tissue typing
Cumulative panel reactive antibody (cPRA)
Cross-match (for living donor work-up)

Infectious disease screening:

- Urine culture
- CMV, EBV and BK virus serology
- Tuberculosis (by 2-step TST or IGRA)
- Hepatitis serology – A, B, C
- HIV serology
- HTLV 1 and 2 serology
- HSV serology
- MMR and varicella serology
- Syphilis serology
- Toxoplasma gondii serology

* Suggested work-up varies by province/transplant program. This list is provided as a reference for labs that are typically requested pre-transplant. Refer to local guidelines for program-specific information.

Table 11.2. Other suggested pre-kidney transplantation work-up*

ECG and echocardiogram
Chest x-ray
Bone age x-ray (if there is growth impairment)
Beta-hCG, PAP smear – for adolescent females
Renal osteodystrophy survey x-ray (RODS)
Lateral spine x-ray, DEXA – performed by some centers
Doppler ultrasound – abdomen/pelvis and lower extremities vasculature
EEG – if a history of seizures
Urodynamic testing, post-void residuals, VCUG – as needed
Urology consult – all patients
Dentistry consult – all patients
Anesthesia consult – all patients
Other specialty consults (e.g. cardiology, infectious diseases) – as needed

* Suggested work-up varies by province/transplant program. Refer to local guidelines for program-specific information.

MANAGEMENT & FOLLOW UP

Early post-operative management:

- Induction immunosuppression
 - Basiliximab or thymoglobulin
- Maintenance immunosuppression for rejection prophylaxis (“triple immunosuppression”)
 - Steroids, calcineurin inhibitor (e.g. tacrolimus) and antiproliferative agent (e.g. mycophenolate mofetil (MMF))
- Medications
 - Anti-infectives
 - Antibiotic prophylaxis e.g. cefazolin
 - Pneumocystis jiroveci pneumonia (PJP) prophylaxis e.g. trimethoprim/sulfamethoxazole
 - ± Antifungal prophylaxis e.g. nystatin
 - ± Antiviral prophylaxis
 - Depends on recipient and donor CMV, EBV and HSV status
 - IV ganciclovir or PO valganciclovir, for at-risk recipients
 - Acyclovir may be used for HSV prophylaxis (if prophylaxis is not required for EBV or CMV)
 - Anticoagulation (depending on recipient and surgical risk factors)
 - Analgesia – acetaminophen, opioids, regional anesthetic blocks
 - Other medications (PPI, bowel regimen, etc.)
- Vigilant urine output monitoring and fluid management to maintain adequate volume status
- Electrolyte monitoring
 - At risk of abnormalities in magnesium, potassium, phosphate, etc.
- Blood pressure and hemodynamic support
 - Initially may require vasopressors to maintain graft perfusion (typically targeting BP around the 95th percentile for age/height)

- Hypertension common after first week – volume overload, corticosteroids, calcineurin inhibitor
- Volume overload management with gradual fluid deficit (diuresis) $\pm$ calcium channel blockers

COMPLICATIONS

The six “ions” of graft dysfunction:

- Rejectionion or progressionion (if graft chronic kidney disease)
- Infectionion (e.g. pyelonephritis, CMV, EBV, BK)
- Dehydrationion
- Medicationion (esp. tacrolimus toxicity)
- Obstructionion
- Detectionion of primary disease recurrence

Acute Rejection

- Clinical features
 - May be subclinical – detectable only by surveillance biopsy
 - Most patients are asymptomatic
 - The first clinical sign is usually an increasing creatinine
 - Creatinine rise $>10\text{-}25\%$ without alternative cause is suspicious
 - Hypertension
 - Signs of graft dysfunction – acidosis, anemia
- Work-up
 - Must exclude the other “ions” before considering rejection
 - Obstruction – doppler ultrasound transplant kidney
 - Infection – cultures, viral testing
 - Dehydration – volume status exam, consider trial of volume resuscitation
 - Medications – review compliance, check drug levels
 - Donor-specific antibody testing

- Graft biopsy
 - For all patients with persistent creatinine elevation without a clear cause
 - Some centers perform routine subclinical rejection surveillance with kidney biopsies (e.g. 3, 6, 12 months)
- Types and basic management
 - Acute T-cell mediated rejection
 - Goal – increase immunosuppression to suppress acute inflammation
 - Strategies
 - High-dose steroids followed by slow taper
 - If no improvement, consider thymoglobulin
 - Optimize maintenance immunosuppression
 - Follow-up – clinical response can only be confirmed with a follow-up biopsy
 - Antibody mediated rejection
 - No consensus guidelines on treatment
 - Goal – remove antibodies and stop antibody production
 - Strategies
 - Plasma exchange
 - High-dose IVIG
 - Anti-CD20 agent (i.e. rituximab)
 - Optimize maintenance immunosuppression

Infection

- Urinary tract infection (UTI)
 - Most common infection post-transplant
 - UTI prophylaxis is considered on a case-by-case basis
- Viral infections
 - EBV, CMV, BK (polyomavirus) are the most significant
 - EBV infection associated with post-transplant lymphoproliferative disorders
 - Anti-viral prophylaxis (e.g. ganciclovir, valganciclovir, acyclovir)

- Depends on recipient and donor viral status, variable duration
- Highest risk is positive donor, negative recipient (i.e. D+ R-)
- General viral infection management
 - Consider reduction of immunosuppression (typically MMF first)
 - Consider anti-viral agents
 - CMV – IV ganciclovir or PO valganciclovir, consider reducing immunosuppression if signs of CMV disease
 - EBV – reduce immunosuppression
 - BK – reduce immunosuppression, consider IVIG and/or leflunomide
 - Other viral infections – varicella, HSV, HPV
- Opportunistic infections – pneumocystis jiroveci pneumonia
 - Trimethoprim-sulfamethoxazole prophylaxis – variable duration
- Fungal infections
 - Some centers recommend nystatin prophylaxis

Other Complications

- *Surgical complications*
 - Bleeding / post-operative hematoma
 - Urinary tract obstruction
 - Urine Leak
 - Wound complications
 - Lymphocele
- *Thrombosis*
 - Highest risk within first week post-transplant
 - Risk factors: young recipient age, hypercoagulability (e.g. nephrotic syndrome), vascular malformations
 - Prevention: early mobilization, if additional risk factors: prophylactic heparin
 - Treatment: therapeutic anticoagulation

- *Primary disease recurrence*

- Certain conditions at risk – FSGS, atypical HUS, membranoproliferative glomerulonephritis, primary hyperoxaluria (if no liver transplant prior to kidney transplantation), lupus nephritis, ANCA vasculitis, IgA nephropathy
- Specific surveillance protocols to detect disease recurrence

- *Hypertension*

- Very common post-transplant, ~ 75% of children require anti-hypertensives
- Potential contributing factors
 - Early
 - Volume overload
 - High dose steroids and tacrolimus
 - Late
 - Steroids
 - Tacrolimus (which causes mineralocorticoid resistance)
 - Renin-angiotensin-aldosterone system activation from hypo-perfused native kidneys
 - Primary disease recurrence
 - Obesity / metabolic syndrome
 - Acute or chronic rejection
 - Chronic allograft vasculopathy
- Work-up
 - Doppler ultrasound of transplant kidney
 - Kidney function and proteinuria assessment
 - Tacrolimus trough level (to exclude toxicity) or area-under-curve (AUC)
 - 24-hour ambulatory BP measurement (ABPM)
 - Echocardiogram to screen for secondary end-organ injury
- Management

- BP target - <90th percentile (< 13 years), or < 130/80 (if ≥ 13 years)
- Dietary sodium restriction, DASH diet
- Regular exercise
- Antihypertensives
 - Calcium channel blockers (1st line agent)
 - Other agents (ACE-inhibitor, beta blockers, others)
- *Post-transplant diabetes*
 - Incidence 1-7%
 - Risk factors: calcineurin inhibitors, steroids, obesity, family history, early dysglycemia (first 30 days)
 - Management: insulin therapy, consider reducing immunosuppression
- *Malignancies*
 - Paediatric kidney transplant recipients are at increased long-term risk of post-transplant lymphoproliferative disorders (PTLD), skin and solid cancers
 - Due to impaired immunological surveillance for malignant cells and suppressed anti-viral functions
 - Cumulative incidence – 7% (by 10 years), 13-15% (by 20 years) and 26-41% (by 30 years)
 - PTLD
 - Closely associated with EBV infection (80% of cases) – leads to B cell transformation and uncontrolled proliferation
 - Management: immunosuppression reduction, rituximab, chemotherapy
 - Skin cancers
 - UV radiation exposure is the most important risk factor
 - HPV infections strongly associated with squamous cell carcinoma risk
 - Prevention: Photoprotection (SPF ≥30 sunscreen, protective clothing), annual skin examination
 - Management: topical therapies, excision, micrographic surgery

- Solid cancers
 - Increased risks of multiple solid cancers (kidney, liver, gastric, etc.)
- Cancer screening – should be prioritized
 - Most cancer screening recommendations not validated in transplant recipients
 - Population screening guidelines may be appropriate for most cancers

IMMUNOSUPPRESSION

- Kidney transplantation is a transition to a new phase of kidney disease. It is not a cure.
- Requires life-long immunosuppression and close surveillance
- The goal of immunosuppression is to optimize allograft survival while minimizing drug toxicities
- Highest degree of immunosuppression within the first three months, gradually tapering to a maintenance level by one-year post-transplant
- *Induction therapy*
 - Rapid and profound immunosuppressive effects
 - Agents used
 - Thymoglobulin (ATG),
 - Typically reserved for cases with a high-risk of early rejection (second transplantation or highly sensitized patients)
 - First dose reactions (flu-like symptoms, fevers)
 - Leukopenia, thrombocytopenia
 - Basiliximab (anti-IL2 antibody)
 - Given immediately prior to transplant (day 0) and on day 4
 - Hypersensitivity reactions
 - No clear consensus recommendations for induction therapy
- *Maintenance therapy*
 - “Triple therapy”

- Steroids
- Calcineurin inhibitor – tacrolimus or cyclosporine
- Antiproliferative agent – MMF or azathioprine
- Modifications to immunosuppression
 - Immunosuppression gradually weaned over the first-year post-transplant
 - Adjustments made based on therapeutic drug monitoring levels
 - Steroid avoidance or minimization protocols also exist
 - May need to decrease if severe leukopenia, viral or other infections
 - May need to increase if acute or subclinical rejection
- Side effects
 - Steroids
 - Typical steroid side-effects (growth impairment, immunocompromise, hypertension, acne, osteopenia, cataracts, hyperglycemia/diabetes, poor wound healing, psychiatric, acne)
 - Tacrolimus
 - Nephrotoxic
 - Hyperkalemia, hypomagnesemia
 - Hypertension
 - Diabetes, hyperlipidemia
 - Neurotoxicity (tremor)
 - Multiple drug interactions! (tacrolimus is metabolized predominantly by cytochrome p450 (CYP3A) – always consult transplant team or pharmacist prior to new prescriptions)
 - Patients advised to avoid grapefruit
 - MMF
 - GI issues (diarrhea, vomiting, abdominal discomfort)
 - Leukopenia, anemia
 - Infections

POST-TRANSPLANT SURVEILLANCE

- Frequent clinic visits initially, gradually reduced to every 2-3 months
- Lab testing – twice weekly initially, gradually reduced to q monthly/q 2 months

Table 11.3. Suggested post-kidney transplant surveillance*

CBC & reticulocytes
Creatinine, urea
Urinalysis, proteinuria (by PCR or ACR)
Bone health – calcium, phosphate, ALP, vitamin D, PTH
Lipid profile
Fasting glucose, HbA1c ± OGTT
Iron studies
Nutritional labs – copper, zinc, selenium
Liver enzymes, albumin, bilirubin
Infectious disease screening: ■EBV, CMV, BK virus ■Hepatitis B and C ■Urine culture
Therapeutic drug monitoring: ■Tacrolimus trough level ■MPA area under the curve (AUC) pharmacokinetic profile
Rejection monitoring: ■Donor-specific antibodies (DSA) ■Surveillance graft biopsy – performed by some centers
Imaging: ■Transplant doppler ultrasound ■Nuclear GFR – performed by some centers
Cardiovascular: ■Blood pressure (BP) – every healthcare visit ■Ambulatory BP monitoring ■ECG and echocardiogram
Bone health: ■DEXA and lateral spine x-ray ■Bone age and RODS
Skin examination, dentistry, ophthalmology – annually

* Frequency of testing varies by province/transplant program. Refer to local guidelines for program-specific information.

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12. THROMBOTIC MICROANGIOPATHY

OVERVIEW

- Thrombotic microangiopathy (TMA) is a histopathological term that describes endothelial cell injury and secondary thrombus formation in small blood vessels. These can occur in any organ but the kidney is predominantly affected. This umbrella term encompasses diseases like thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (STEC HUS and atypical HUS) and lots of secondary forms of TMA.
- Hemolytic uremic syndrome (HUS) is a term coined by pediatricians that describes the clinical findings of patient with TMA, which includes hemolytic anemia and kidney failure (uremia), including STEC HUS and atypical HUS.
- HUS is a common cause of acute kidney injury in North America in otherwise healthy children.

Table 12.1 Causes of TMA

Genetic/ Autoimmune	Associated with Infections	Associated with Autoimmune Diseases	Post- Transplant	Associated with other kidney diseases	Others
• aHUS • DGKE HUS • Pregnancy / Postpartum/ HELLP syndrome • TTP	• STEC HUS • Pneumococcal HUS • Influenza • HIV • VZV • Bordetella pertussis	• SLE • APS /CAPS • Scleroderma • Dermatomyositis • AAV	• TMA post BMT/SCT • TMA post-solid organ transplantation	• C3G/MPGN • Membranous Nephropathy • IgA Nephropathy	• Malignancy/ Chemotherapy • Drugs (CNI, sirolimus, anti-VEGF agents) • Malignant hypertension • Cobalamin C deficiency • unexplained

MAKING THE DIAGNOSIS

1. Hints on history/examination: Diarrhea including bloody diarrhea, fatigue, pale, decreased urine output, petechiae, recent intake of raw/uncooked meat, visit to farm
 - Post-bone marrow transplantation, consider this diagnosis if severe hypertension, and proteinuria and edema
2. Triad of microangiopathic hemolytic anemia (DAT negative), thrombocytopenia and renal insufficiency. Hemolysis is indicated by elevated LDH, hyperbilirubinemia, low/undetectable haptoglobin.
3. Further investigations to determine underlying cause:
 - Send for: C3/C4, ADAMTS13 activity (to rule out TTP), stool for EHEC and Shiga toxin (for STEC HUS)
 - Optional investigations depending on symptoms: blood culture, viral serology, complement genetics and CFH antibodies

ETIOLOGIES

STEC HUS

- 90% of cases in childhood TMA, especially in children < 10 years of age
- Caused by Shiga toxin–producing strains of enterohemorrhagic *Escherichia coli* (EHEC), e.g. O157:H7
- Cattle are the main hosts for EHEC, Shiga toxin is contained in their feces (feco-oral route). Infections occur after eating raw/undercooked beef, petting of animals or consumption of contaminated foods/fluids.
- Presents with abdominal pain followed by diarrhea (often bloody diarrhea), renal symptoms develop 2–7 days after onset of diarrhea.
- Pathogenesis: Shiga toxin translocates into the blood stream and binds to its receptor Gb3, primarily on kidney endothelial cells. There it inhibits protein synthesis causing endothelial cell injury and damage.
- It is unclear why mainly children are affected, except for outbreaks.
- Monitor for other organ involvement:
 - CNS symptoms include seizures, decreased level of consciousness, encephalopathy, hallucinations and headache.

- GI manifestations: pancreatitis, transaminitis, enterocolitis and abdominal pain.
- Cardiac dysfunction or multi-organ failure are rare, but can be fatal
- Predictors for poor outcome include CNS involvement, hyponatremia, leukocytosis and hemoconcentration at initial presentation.
- Treatment is supportive:
 - Avoid use of anti-microbials
 - If hemodynamically unstable or if significantly anemic the patient should receive RBC transfusion.
 - Platelet transfusions should not be given routinely, unless the patient is actively bleeding or if a procedure is required.
 - Supportive measures: fluid and dietary restriction (potassium and/or phosphate), treatment of hypertension and if needed treatment of potentially life-threatening electrolyte disorders (i.e. hyperkalemia). Monitoring of fluid inputs and outputs is critical to avoid fluid overload.
 - Note, complement blockers may be considered if neurological involvement or severe extra-renal complications.
 - Short-term dialysis may be needed in up to 2/3 of patients. ESKD reported in 5%.
 - Mortality: 2-4%
- Overall good long-term prognosis and no recurrence post-transplant. However, patient needs long-term follow up as 20% develop proteinuria/hypertension > 5 years of initial disease and may be at risk of developing CKD.

Atypical HUS

- Due to genetic mutations in complement components (majority are sporadic) or autoantibodies. Mutations or antibodies result in over-activation of complement, leading to endothelial cell activation, C5b-9 insertion on endothelial cells and subsequent injury and TMA.
- Presents similarly to STEC HUS, usually triggered by infection such as URTI, gastroenteritis including non-bloody diarrhea (bloody diarrhea points more towards STEC HUS).
- 30-60% of patients have low C3 and normal C4.

- Treatment with complement-blocker (anti-C5 antibody, i.e. eculizumab) if available, otherwise therapeutic plasma exchange.
 - Of note, patients require meningococcal vaccination prior to starting treatment with eculizumab due to increased risk of meningitis
- Treatment with complement blocker has significant improved outcome, with recovery from acute episodes and prevention of disease recurrence in native and transplanted kidneys.
- Patient with CFH-antibodies are treated with TPE followed by immunosuppression
- Additional supportive measures as mentioned with STEC HUS.
- Short- term dialysis might be needed.
- Mortality 6-8%
- Long-term outcome depends whether patient is treated with complement blocker or not.
 - Outcome with TPE and risk for recurrence in native and transplanted kidneys depend on genetic mutation, but overall 30% at 1 year either have ESKD or died and disease recurrence rates are up to 80%.
 - Complement blockade prevents ESKD for years and allows for transplantation even in high-risk patients without recurrence.

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4

SECTION 4

Structural, Urological and Tubular disorders
in Paediatric Nephrology

OUTLINE

- 13. CAKUT and Cystic Kidney Disease
- 14. Urolithiasis
- 15. Tubular Disorders
- 16. Urinary Tract Infections and VUR

Abbreviations

CAKUT = congenital anomalies of the kidney and urinary tract

ACEI = Angiotensin converting enzyme inhibitor

ARB = Angiotensin receptor blocker

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

US = ultrasound

BP = blood pressure

MCDK = multicystic dysplastic kidney

ADPKD = autosomal dominant polycystic kidney disease

ARPKD = autosomal recessive polycystic kidney disease

HTN = hypertension

UTI = urinary tract infection

CKD = chronic kidney disease

NPHP = nephronophthisis

ANH = antenatal hydronephrosis

PUV = posterior urethral valve

FTT = failure to thrive

FHHNC = familial hypomagnesemia with hypercalciuria and nephrocalcinosis

CT = computed tomography

NSAID = non-steroidal anti-inflammatory drugs

MET = medical expulsive therapy

RIRS = retrograde intra-renal surgery

CAM = complementary and alternative medicines

RTA = renal tubular acidosis

HCO₃ = bicarbonate

DMSA = Dimercaptosuccinic acid

13. CAKUT AND CYSTIC KIDNEY DISEASE

- CAKUT (congenital anomalies of the kidney and urinary tract) - broad variety of disorders that result from abnormal development during intrauterine life
- Incidence: ~1:500 live births
- Can occur as a part of a genetic syndrome or a chromosomal disorder
- Environmental factors include exposure to teratogens, e.g. ACEI, ARBs.
- Outcome depends on amount of functioning kidney tissue and associated urological complications

UNILATERAL KIDNEY AGENESIS

- Congenital absence of kidney tissue
- 1/3 have additional CAKUT, 1/3 have additional extrarenal manifestations e.g. cleft lip/palate, preauricular pits, cardiac and vertebral defects
- Investigations: VCUG if recurrent UTI's
- Monitoring: Kidney US, BP and urine dipstick, blood work as clinically indicated
- Prognosis: good if single kidney is otherwise normal and shows compensatory growth.
Long-term: 40% incidence of hypertension and 20% incidence of proteinuria

HYPOPLASTIC KIDNEY

- Small kidney(s) due to reduced number of otherwise normal nephrons
- Monitoring: Kidney US, BP and urine dipstick, blood work as clinically indicated
- Prognosis: Clinically significant if both kidneys affected; can progress to end-stage kidney failure by late childhood

DYSPLASTIC KIDNEY

- Kidney lacks normally developed nephron structures

- Monitoring: Kidney US, BP and urine dipstick, blood work as clinically indicated
- Prognosis: Extent of kidney dysfunction depends on degree of abnormalities

MULTICYSTIC DYSPLASTIC KIDNEY

- Second most common cause of flank mass in newborn
- Results from abnormal metanephric differentiation; MCDK is non-functional.
- Contralateral kidney may have limited dysplasia and/or VUR, bilateral MCDK is rare and presents with newborn kidney failure and lung hypoplasia which may not permit survival
- Monitoring: Kidney US to monitor kidney size (involution of multicystic dysplastic kidney and compensatory growth of contralateral kidney), BP and urine dipstick, blood work as clinically indicated
- DMSA scan helpful to confirm non-functional kidney if unclear diagnosis of MCDK
- Prognosis: Good if contralateral kidney shows compensatory growth

ABNORMALITIES OF POSITION

- Includes ectopic, horseshoe, crossed fused ectopia
- Prognosis: Few long-term consequences unless associated with dysplasia, reflux, or obstruction

HYDRONEPHROSIS

- Hydronephrosis is a dilatation of the renal collecting system. Other definitions related to hydronephrosis:
 - Pelviectasis: dilated renal pelvis.
 - Pelvicaliectasis: dilated renal pelvis and calyces, associated with parenchymal thinning
 - Caliectasia – dilation of the calyces; termed hydrocalyx if only one calyx is dilated
 - Hydroureter/Megaureter – dilation of the ureter
 - Obstruction – an impediment to urinary flow, which if uncorrected will limit the ultimate functional potential of a kidney

- Antenatal hydronephrosis (ANH) is a common abnormality seen on fetal US (every 100-500 pregnancy)
- **Definition:** different grading systems are used at different institutions (3 highlighted below).

1. Anteroposterior renal pelvic diameter (APD):

	2nd Trimester	3rd Trimester
Mild	4-6mm	7-9mm
Moderate	7-10mm	10-15mm
Severe	>10mm	>15mm

- Abnormal: >4 mm in second trimester and/or >7 mm in third trimester and >10mm after birth (>48h)

Table 13.1 Adapted from: *Nguyen HT, et al. The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010;6:212-231*

2. Severity grading via SFU (Society of Fetal Urology):

Grade 1: Slight splitting of central renal complex -> 97% resolution

Grade 2: Central renal complex splitting confined to renal border, normal parenchyma -> 50% spontaneous resolution & 40% surgery

Grade 3: Wide splitting, pelvis dilated outside renal border, caliectasis, normal parenchyma -> 60% requiring surgery

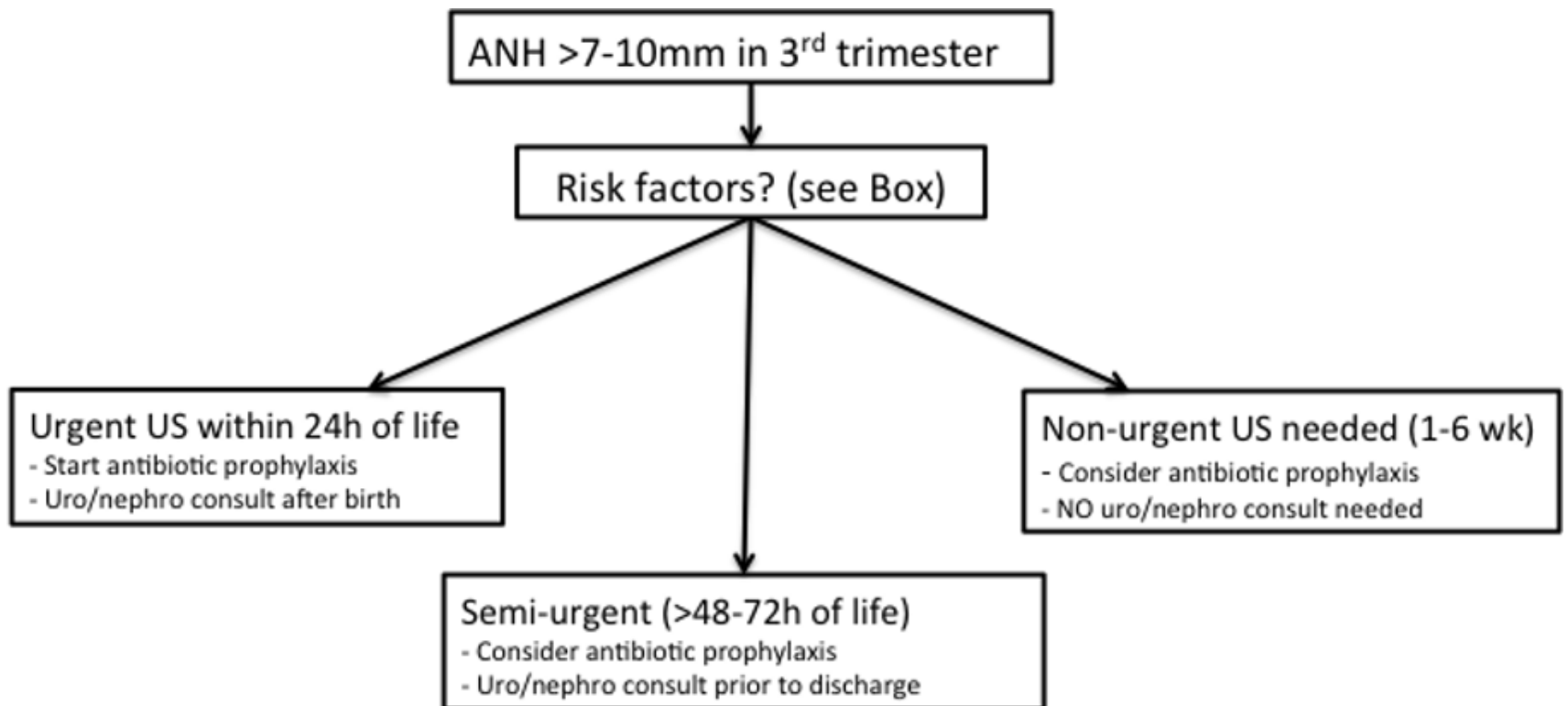
Grade 4: Pelvicaliectasis with thinning of the border -> 75-100% need surgery

3. UTD Classification system

- Risk stratification based on combination of APD, presence of central vs. peripheral calyceal dilatation, abnormal ureter, abnormal bladder, parenchymal thickness or appearance abnormality, unexplained oligohydramnios.
- Differential diagnosis of antenatal hydronephrosis:
 - Transient (not seen on postnatal US) - 41-88%
 - UPJ obstruction - 10-30%

- VUR - 10-20%
- UVJ obstruction/megaureter - 5-7%
- Other: MCDK , PUV/urethral atresia, Prune-belly syndrome, cystic kidney disease, congenital ureteric stricture, megalourethra – uncommon
- Management:
 - Please follow local guidelines from your center as management varies.
 - Kidney and bladder US:
 - In all neonates with isolated antenatal hydronephrosis (>10mm in 3rd trimester) and/or any urinary tract abnormalities (hydroureter, abnormal bladder)
 - Prior to discharge in patients with: ANH in single kidney or bilateral ANH, or dilated bladder consistent with PUV, severe unilateral hydronephrosis leading to pulmonary mass effect
 - In others: 1 - 6 weeks of life (avoid US < 48-72h of life as neonates have low urine output)
 - Indications for VCUG: concern for bladder outlet obstruction (PUV), severe bilateral hydronephrosis. May consider VCUG if dilated ureter, unilateral severe hydronephrosis, duplex kidney with hydronephrosis.
 - Antibiotic prophylaxis: consider starting in newborns with >10-15mm APD on prophylaxis until postnatal kidney US done (e.g. 2-5mg trimethoprim/kg/dose PO once daily or amoxicillin 25 mg/kg/day once daily or according to local guidelines and resistance profile)

Algorithm for ANH after Birth



Risk factors for urgent evaluation:

- Severe ANH in single kidney
- Severe ANH bilateral
- Dilated bladder consistent with PUV
- Severe unilateral hydronephrosis leading to pulmonary mass effect

Risk factors for semi-urgent evaluation:

- Moderate ANH in single kidney
- Moderate ANH bilateral
- MMC
- Duplex kidney with ectopic ureter or ureterocele

*severe ANH if APD > 15mm

UPJ OBSTRUCTION

- Functionally significant impairment of urinary flow from renal pelvis to ureter
- Cause:
 - Congenital narrowing of ureteropelvic junction (UPJ, *most common in newborns and infants*)
 - External compression from aberrant vessels or muscular bands (present later in childhood, rare)
 - Acquired e.g.: stones, postoperative or inflammatory stricture, urothelial cancer, external compression

- Clinical presentation: most cases diagnosed on antenatal screens, if not
 - Children may present with an abdominal mass, UTI or in older children with symptoms of loin pain +/- nausea and vomiting, hematuria.
 - 75% unilateral, up to 50% have other urological anomaly, e.g. MCDK, renal agenesis, VUR, horseshoe kidney
- Investigations: kidney US will show hydronephrosis, can rule out other causes of obstruction (e.g. stone). Lasix washout (diuretic renography/MAG-3 scan) scan to assess differential renal function and degree of obstruction
- Management: conservative with regular US screening, but 1/3 will need surgery
 - Indications for intervention: worsening symptoms or hydronephrosis on serial US, impaired renal function, stones, infection, hypertension
 - Surgery: surgical removal of obstructed segment and re-anastomosis of ureter to renal pelvis (pyeloplasty)
 - Percutaneous nephrostomy if needed for urgent decompression

UVJ OBSTRUCTION

- Obstruction at the ureterovesical junction (cause still unknown)
- Clinical presentation:
 - Can be diagnosed antenatal as hydroureter or hydro-ureteronephrosis
 - Ddx: adynamic ureter, which can look like a partial obstructive picture)
 - Postnatal can present with recurrent UTI
- Investigations: Kidney and bladder US, depending on severity, further work-up might include VCUG and MAG-3 scan
- Management: conservative but some might need surgery
 - Indications for intervention: symptomatic or impaired function on MAG-3/DMSA scan)
 - Surgery: ureteric reimplantation

VESICoureteral Reflux

- See [chapter 16](#).

POSTERIOR URETHRAL VALVES

- Valves in posterior urethra obstruct urine outflow from bladder
- Most common cause of bladder outlet obstruction, majority of boys with PUV will develop bladder dysfunction/failure over time
- Wide spectrum of clinical presentation:
 - Mild: straining to urinate, weak urinary stream, frequent UTIs, failure to pass urine in the first 24 h of life, palpable bladder
 - Severe: usually presents in-utero with hydroureteronephrosis, +/- oligohydramnios and early CKD. Pulmonary hypoplasia (Potter sequence) may not be compatible with life.
- Investigations:
 - antenatal US shows thick dilated bladder and “keyhole” sign, bilateral hydroureters and hydronephrosis
 - VCUG: thickened and trabeculated bladder, bladder diverticuli, hypertrophied bladder neck, dilated posterior urethra, can have associated VUR
 - Urethroscopy
 - Renal function and electrolytes
- Management:
 - Immediate bladder decompression via bladder catheter, or stent
 - Definitive treatment: surgical ablation of valves is treatment of choice, cutaneous vesicostomy if primary ablation not possible or persistent obstruction
 - Treat renal failure and electrolyte abnormalities
 - May need clean intermittent catheterization (CIC)
- Prognosis: Progression of CKD is determined by underlying dysplasia, urinary tract infections, the presence of high bladder pressures, and compliance for follow-ups. Rapid worsening of kidney function may occur at the time of puberty. Near normal kidney function at 1 year of age is good prognostic marker.

PRUNE BELLY SYNDROME

- Characterized by absent abdominal wall musculature, urinary tract anomalies and bilateral intra-abdominal cryptorchidism
- Wide spectrum of clinical presentation
 - Urological anomalies range from mild (urinary tract dilatation) to severe (renal failure), 50% have renal dysplasia.
 - Associated malformations include: orthopedic (club feet), GI (malrotation) and cardiopulmonary
 - Most cases are sporadic and have normal karyotype
 - Predominantly seen in boys
- Investigations:
 - Renal US and VCUG: big bladder with wide bladder neck (PUV small bladder neck), smooth bladder wall (in PUV trabeculated)
- Management:
 - Extra-GU issues including orchidopexy and sometimes surgical management of abdominal wall laxity
 - Monitoring of urine output and renal function
 - UTI prevention: circumcision, antibiotic prophylaxis sometimes needed
 - Often require intermittent catheterization

KIDNEY CYSTS

- A cyst is an epithelium-line cavity filled with fluid.
- Cysts in the kidney may be inherited or acquired.
- Cysts can be unilateral (simple cyst, MCDK) or bilateral. Bilateral cysts are further differentiated whether they occur in small/normal sized kidneys (medullary cystic disease, nephronophthisis) or large kidneys (most likely polycystic kidney disease)
- Syndromes associated with kidney cysts: Tuberous sclerosis, von Hippel-Lindau disease, VACTERL association, Smith-Lemli-Opitz, Branchio-oto-renal, HNF1b-related kidney disease

GENETIC CYSTIC KIDNEY DISEASES

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Most common inherited kidney disease, incidence: 1 in 500
- Mutations in PKD1 (Type 1, 85%) or PKD2 (Type 2), GANAB and DNAJB11
- Kidney cysts throughout nephron, often larger, macroscopic cysts
- Variable presentation, even within a family but kidney function usually normal throughout childhood, found on US screening in family known to have disease or presents in adulthood with HTN and kidney dysfunction/kidney failure
- Kidney symptoms include hypertension (HTN), urinary tract infection (UTI)/pyuria, proteinuria, gross or microscopic hematuria, flank mass, urolithiasis, chronic kidney disease
- Extra-renal symptoms include mitral valve prolapse, GI diverticuli, cerebral aneurysm, hepatic, pancreatic, ovarian and seminal vesicle cysts
- Diagnosis made with clinical findings, imaging and positive family history (disease or gene mutation in one parent) – negative US does not rule out ADPKD until the 4th decade of life
- Screening ultrasound of parents of index case or grandparents if parents younger than 30 years.
- Patient monitoring: if asymptomatic, US screening every few years; more frequently once symptomatic, annual BP and urinalysis, may consider MRI in patients >16 to screen for intracranial aneurysm
- Prognosis: ESKD in 60-70% by 6th decade of life
- Treatment: ACEI for hypertension and/or proteinuria. Aquaporin inhibition (Vaptans) is recommended for adult patients, but is not currently approved for use in children.

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- Mutations in PKHD1 and rarely DZIP1L
- Incidence 1:20,000
- Characterized by polycystic kidneys and congenital hepatic fibrosis, cysts often smaller, may have severe liver disease with bile duct dilatation (Caroli disease)
- Majority present in infancy, antenatal US may show enlarged kidneys with loss of corticomedullary differentiation and oligohydramnios +/- pulmonary hypoplasia. Older

children may present with large palpable flank mass, hypertension, recurrent UTI, polyuria or CKD.

- Extrarenal symptoms include respiratory insufficiency with history of oligo/anhydramnios, hepatosplenomegaly, esophageal varices, hypersplenism and liver failure
- Diagnosis based on clinical findings, imaging and family history (absence of cysts in both parents but may have affected sibling)
- Monitoring: Kidney and liver US at least yearly, endoscopy for esophageal varices
- Prognosis: worse than ADPKD, CKD and ESKD develops quite early – the majority in childhood, also liver fibrosis can be severe
- No specific treatment. Supportive management for hypertension and CKD

Nephronophthisis (NPHP)

- NPHP is the most common genetic cause of ESKD during childhood and adolescence.
- Several NPHP genes have been identified, can occur as kidney limited or syndromic cerebello-ocular-renal disorders like Senior-Løken syndrome, Joubert syndrome, Bardet-Biedl syndrome, and Meckel-Gruber syndrome.
- Forms:
 - Infantile – usually presents with ESKD in 1-3 year of life, US shows enlarged kidneys with microcysts in cortex
 - Juvenile – usually presents with polyuria/polydipsia or secondary enuresis, ESKD by 2nd decade of life, US shows normal-sized echogenic kidneys with small cortical cysts, most common form
 - Adolescent - usually presents with ESKD around 20 years
- Supportive CKD treatment, genetic testing, management of hypertension especially in infantile form

Medullary Cystic Kidney Disease

- AD, mutations in MCKD1 and 2
- Usually presents in adulthood
- Ultrasound shows normal-sized kidneys, which are echogenic with small cysts at the corticomedullary junction.

FURTHER READING

Capolicchio, John-Paul, Luis H. Braga, and Konrad M. Szymanski. Canadian Urological Association/Pediatric Urologists of Canada guideline on the investigation and management of antenatally detected hydronephrosis. *Canadian Urological Association Journal* 2018;12.4: 85.

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14. UROLITHIASIS

OVERVIEW

- More common in boys in the first decade (due to urinary tract anomalies) and girls in the second decade (due to UTI, metabolic and dietary risk factors)
- Up to 80% of children have detectable risk factors for urolithiasis

ETIOLOGIES

Metabolic abnormalities (~50%)

- Solute excess – high concentration of a “lithogenic” solute (e.g. calcium, oxalate, uric acid, cystine, sodium)
- Decreased urine stone inhibitors (e.g. citrate, magnesium)
- Low urine volume (seen in two-thirds of paediatric cases)

Types of metabolic abnormalities leading to stone formation:

- *Hypercalciuria* (30-50%)
 - Idiopathic hypercalciuria (most common, may be related to excess salt intake)
 - Dent disease (and Lowe syndrome)
 - Bartter syndrome
 - Distal renal tubular acidosis
 - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)
 - Immobilization (bone resorption)
 - Medications (loop diuretics, steroids)
 - Conditions associated with hypercalcemia
 - Hyperparathyroidism
 - William's syndrome
 - Vitamin D intoxication or deficiency

- Idiopathic infantile hypercalcemia
- *Hyperoxaluria* (10-20%)
 - Primary hyperoxaluria (types 1, 2 and 3)
 - Rare genetic disorders, overproduction of oxalate and glycolate
 - Results in recurrent kidney stones and progressive renal impairment
 - Some patients respond to pyridoxine (vitamin B6)
 - Definitive treatment is combined liver/kidney transplant
 - Secondary hyperoxaluria
 - Increased enteric oxalate absorption, due to fat malabsorption or intestinal inflammation
 - Excess fatty acids bind calcium in GI tract = less available calcium to bind oxalate = more free oxalate absorption
 - At-risk conditions
 - Inflammatory bowel disease
 - Short bowel syndrome
 - Pancreatitis
 - Cystic fibrosis
 - Enteric oxalate absorption may also be increased by low calcium intake
- *Hypocitraturia* (10%)
 - Citrate is an inhibitor of calcium oxalate and calcium phosphate stone formation, by binding calcium in the tubular lumen (soluble complex)
 - Associated with high animal protein and low fruit/vegetable diet
 - Also seen in chronic metabolic acidosis (due to tubular citrate reabsorption)
 - E.g. chronic diarrhea, renal tubular acidosis, ketogenic diet and topiramate/acetazolamide use
- *Hyperuricosuria* (2-10%)
 - Idiopathic hyperuricosuria (commonly familial), often associated with hypercalciuria
 - Pure uric acid stones – uncommon in children
 - Tumour lysis syndrome

- Lymphoproliferative and myeloproliferative disorders
- Uric acid metabolism disorders – e.g. Lesch-Nyhan syndrome

Other causes of stone formation

- *Cystinuria* (5%)
 - Autosomal recessive disorder, excessive tubular excretion of dibasic amino acids (cystine, arginine, lysine, ornithine)
 - Causes recurrent nephrolithiasis (often positive family history)
- *Infection* (~ 20%)
 - May cause stone formation or occur as a result of stone presence
 - More common in the setting of functional or anatomical obstruction
 - Urease-producing organisms
 - Proteus, Providencia, Klebsiella, Pseudomonas, Enterococci
 - Causes struvite stone formation, which can enlarge to fill renal calyces (“Staghorn calculi”)
- *Structural or functional* (10-20%)
 - Any cause of urinary stasis can predispose to stone formation, including:
 - UPJ obstruction
 - Horseshoe kidney
 - Bladder exstrophy
 - Bladder augmentation
 - Neurogenic bladder
- Other risk factors
 - Prematurity and low birthweight (higher risk of nephrocalcinosis)
 - Neurological disorders (reduced fluid intake, immobility and bone resorption, exposure to antiepileptics such as topiramate, or ketogenic diet)
 - Dietary factors (numerous and variable depending on stone composition)

MAKING THE DIAGNOSIS

Clinical Presentation

- Incidental finding / asymptomatic (~ 20% of children)
 - More common in infants and young children
 - More common for stones located in the kidney (vs. ureter or bladder)
- Pain – abdominal or flank (~ 50-75%)
 - Ranges from mild to severe debilitating “renal colic” episodes
 - Often recurrent, diagnosis may be delayed
- Gross hematuria (up to 30%)
- Dysuria and urgency (~ 10%) – may be associated with bladder stone or UTI
- Stone passage (~ 5%) – uncommon first presentation
- Persistent nausea/vomiting – commonly associated with pain

Historical Clues

- Personal history of...
 - Previous kidney stones
 - Urinary tract anomalies or functional disorders
 - Other metabolic disorders
 - Recurrent UTI – important to find out which organisms
 - Non-traumatic bone fracture
 - Delayed motor milestones or muscle weakness
 - Delayed or abnormal tooth development
- Medications – e.g. furosemide, steroids, topiramate, acetazolamide, recent antibiotic use
- Dietary history
 - High sodium and animal protein intake
 - Low calcium intake
 - Ketogenic diet
 - Vitamins (especially C and D) and nutritional supplements

- Low daily fluid intake – important to precisely quantify
- Family history
 - Consanguinity
 - Kidney stones (high risk of metabolic disorder if first degree relative affected at a young age)
 - Other genetic/metabolic disorders

Physical Examination

- Vital signs – normal BP? Fever? Is this child unwell?
- Growth parameters
- Dysmorphic features
- Mobility status
- Musculoskeletal deformities including rickets or craniosynostosis
- Abnormal genitalia
- Abdominal exam – to rule out other causes of abdominal pain

Initial Work-Up (to confirm urolithiasis)

- Urinalysis
 - Hematuria/proteinuria
 - Urine pH
 - Acidic urine – increased risk of cystine and urate stones
 - Alkaline urine – increased risk of struvite and calcium phosphate stones
 - Urine specific gravity (<1.020 = adequate hydration, 1.020-1.030 = hypohydrated, >1.030 = dehydrated)
 - Signs of UTI
- Urine microscopy (if available; for uric acid and cystine crystals)
- Urine culture – for all patients, to exclude UTI
- Imaging
 - Kidney/bladder ultrasound – recommended 1st line paediatric imaging

- ~ 80-90% sensitivity (false negatives: small stones, calyceal or distal ureteral stones)
- Abdominal x-ray
 - Not routinely recommended (sensitivity ~ 60%)
- Non-contrast CT
 - Gold-standard diagnostic test (sensitivity >95%)
 - Reserved for children with suspected stones based on symptoms or signs of obstruction on ultrasound but no stone visualized)

Metabolic Stone Work-Up

- All children with urolithiasis should undergo stone screening – typically performed under the supervision of a paediatric nephrologist
- Stone composition
 - Send any fragments or passed stones for lab analysis
 - Helps guide further testing and treatment decisions
- Blood testing
 - Creatinine, urea
 - Sodium, potassium, chloride
 - Calcium, phosphate, magnesium
 - Bicarbonate
 - Urate
 - $\pm$ ALP, PTH, 25-OH vitamin D and 1,25-OH vitamin D (if abnormal serum Ca, PO₄ or hypercalciuria)
- Spot urine – sodium nitroprusside test (screen for cystinuria) or urine amino acids
- 24 hour urine testing
 - Urine volume and creatinine (to determine sample adequacy)
 - Calcium
 - Oxalate
 - Citrate
 - Uric acid

- Magnesium
- Additional tests to consider (specific situations):
 - Sodium
 - Cystine (if positive nitroprusside screen)
 - Phosphate
 - Protein / beta-2-microglobulin (if Dent's disease suspected)
- If a 24 hour urine collection is not feasible (i.e. infant / young child)
 - Spot urine screening can be performed

Table 14.1. Normal urine values for 24 hour urine collection

Urine Constituent	Age	24 hour urine value
Calcium	All ages	<0.1 mmol/kg
Oxalate	>2 years	<0.5 mmol/1.73m ²
Citrate	All ages	>0.94 mmol/1.73m ² >1.3 mmol/1.73m ²
Uric acid	All ages	<0.11 mmol/kg/day <800 mmol/1.73m ²
Magnesium	All ages	>0.04 mmol/kg
Cystine	<10 years >10 years	<55 micromol/1.73m ² <200 micromol/1.73m ²

Table modified from: Geary DF and Schaefer F. *Pediatric Kidney Disease.*; 2016. Accessed November 23, 2020. <https://doi.org/10.1007/978-3-662-52972-0>.

Table 14.2. Normal urine values for spot urine collection

Urine constituent	Age	Spot urine value (mmol/mmol creatinine, unless otherwise stated)
Calcium	<1 year	<2.2
	1-3 years	<1.5
	3-5 years	<1.1
	5-7 years	<0.8
	>7 years	<0.7
Oxalate	0-6 months	<0.37
	7-24 months	<0.26
	2-5 years	<0.14
	6-12 years	<0.08
	>16 years	<0.04
Citrate	All ages	>0.1 urine calcium:citrate $\geq$ 1.6 mmol/ mmol (increased risk of stone formation)
Uric acid	<2 years	<0.18 mmol/L GFR*
	>2 years	<0.03 mmol/L GFR
Cystine	<1 month	<85 mmol/mol
	1-6 months	<53 mmol/mol
	>6 months	<18 mmol/mol

* Calculated by multiplying the ratio of the urine uric acid/creatinine by the serum creatinine

Table modified from: Geary DF and Schaefer F. *Pediatric Kidney Disease.*; 2016. Accessed November 23, 2020. <https://doi.org/10.1007/978-3-662-52972-0>

MANAGEMENT & FOLLOW UP

Acute Management

- Indications for hospitalization
 - Urinary tract obstruction with AKI
 - Urinary tract obstruction with solitary kidney
 - Need for IV fluids or analgesia to manage symptoms
 - Urosepsis / pyelonephritis
- Medical management
 - IV fluids (if oral fluid intake reduced or dehydrated)
 - Analgesia
 - NSAIDs e.g. ketorolac (avoid if patient has an AKI, is at-risk of developing an AKI or chronic kidney disease)
 - Acetaminophen
 - Opioids (e.g. morphine, as needed for severe pain)
 - Antibiotics (if concomitant UTI)
 - If urosepsis + obstructed stone – requires emergent drainage with ureteral stent or percutaneous nephrostomy
 - Medical expulsive therapy (“MET”)
 - Alpha-blockers (tamsulosin), calcium channel blockers
 - Shown in systematic reviews to increase likelihood of ureteral stone passage in children, reduce hospitalization and need for surgical intervention
 - Consider for children >2yr with distal ureteral or bladder stone (< 10mm)
- Stone passage
 - Likelihood of spontaneous passage decreases with increasing stone diameter
 - < 5mm – likely to pass (~ 80%), 5-10mm – might pass (~ 60%), > 10mm – unlikely to pass spontaneously
 - Observation period (typically 2-4 weeks)

- Reasonable approach for any asymptomatic and non-obstructing stones (< 10mm)
- Instruct families to strain urine while symptomatic to collect any stone fragments that are passed (can use a reusable coffee filter with a fine mesh or an aquarium fish net)
- If no stone passage by 4 weeks (by “stone in hand” or ultrasound, consider surgical removal)

Urological Interventions

- Indications
 - Urinary tract obstruction + acute kidney injury or solitary kidney
 - Suspected infected stone
 - Struvite stones
 - Severe unremitting pain
 - Symptomatic stones failing a trial of observation
 - Consider for asymptomatic large stones (> 10mm)
- Procedures
 - Extracorporeal shockwave lithotripsy
 - Ureteroscopy / retrograde intra-renal surgery (RIRS)
 - Percutaneous nephrolithotomy
 - Open surgery

Stone Prevention

- Recommendations for all patients
 - Increase fluid intake
 - Increases urine flow rate and lowers urine solute concentrations
 - Compliance with fluid intake prescription is a major issue!
 - Minimum fluid intake – 1.5-2L / m² / day
 - Target 24-hour urine volume
 - Infants > 750mL
 - 1-5 years > 1000mL

- 5-10 years > 1500mL
- > 10 years > 2000mL
- Normalize dietary intake
 - Reduce sodium intake to recommended dietary allowance (RDA)
 - Avoid excessive animal protein, vitamin C or D intake
 - Normal dietary calcium is important (low and high calcium intake both predispose urolithiasis)
 - Increase fruit and vegetable intake (sources of citrate and potassium)
- Stop or wean any offending medications
- Complementary and alternative medicines (CAM)
 - Multiple therapies proposed, especially in traditional Chinese medicine
 - Inadequate efficacy and/or safety data to recommend any CAM therapies for paediatric urolithiasis

Table 14.3. Specific metabolic interventions for stone prevention

Metabolic abnormality	Dietary measures	Medications
Hypercalciuria	• Normal sodium diet • Normal calcium diet • Avoid vitamin D supplementation (unless deficient)	If no response to dietary measures over 3-6 months: • Thiazide diuretics • Amiloride • Potassium citrate or magnesium citrate
Hyperoxaluria	• Avoid high oxalate foods (e.g. tea, sweet potatoes, pepper, chocolate, spinach, nuts, citrus peel) • If fat malabsorption: low fat diet, magnesium supplement, consider cholestyramine	• Calcium carbonate or acetate with meals (as oxalate binder) • Pyridoxine (if primary hyperoxaluria suspected) • Potassium citrate

Hypocitraturia	• Lemon, lime, orange and grapefruit juices (add fresh lemon juice to additional daily fluid intake!) • Reduce animal protein intake	• Potassium citrate, magnesium citrate, or calcium citrate (if calcium supplement needed)
Hyperuricosuria	• Increase fluid intake • Restriction of dietary purines (e.g. anchovies, mussels, liver, kidney) – not an issue for most children!	• Urinary alkalization (target urine pH 6.5-8.0) with citrate supplementation • Allopurinol (if uric acid metabolism disorder) • Rasburicase (in tumour lysis syndrome)
Cystinuria	• Increase fluid intake • Low sodium diet	• Urinary alkalization (target urine pH 7.5-8.0) with citrate supplementation • Tiopronin or D-penicillamine for severe cases • Captopril (if also hypertensive)

Follow-Up

- Surveillance – to detect stone growth and new stones (“increasing stone burden”)
 - Frequency depends on stone size, location, number, evidence of obstruction
 - Ultrasound imaging – primary modality for stone surveillance
 - Typically done every 6-12 months to re-evaluate stones
- Metabolic testing
 - Should be repeated 2-3 months after implementation of metabolic interventions to determine effect and need for additional measures
 - Once metabolic abnormalities corrected, should be repeated every 1-2 years
 - 24 hour urine collection (if feasible), otherwise repeat spot urine collection is a reasonable alternative

- Prognosis
 - Stone recurrence is common (20-30%), more common if underlying metabolic abnormality
 - Limited evidence regarding impact of urolithiasis on long-term kidney function – some data suggests a higher risk of chronic kidney disease among stone-formers
 - Theoretical mechanisms for adverse kidney outcomes (e.g. renal scarring, intermittent obstruction, recurrent UTI, nephrocalcinosis)
 - Regular kidney surveillance (BP, urinalysis and serum creatinine) should be considered, particularly for patients with high stone burden or complications as there is a risk of hypertension and CKD long-term

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15. TUBULAR DISORDERS

GENERAL APPROACH

Thorough history including:

- Polyuria/nocturia, polydipsia?
 - Feature of many tubular disorders. Needs to be distinguished from frequent sipping and urinary frequency, in which case both volumes are low.
- Oliguria/anuria?
 - Relevant for acute kidney injury, will assist in determining next steps
- Low energy, low appetite, weight loss? Failure to thrive or poor growth?
 - These may be indicative of persistent metabolic acidosis
- Recurrent vomiting
 - Seen in persistent metabolic acidosis
- Visual difficulties
 - Impaired visual acuity or retinopathy can be associated with cystinosis and other tubulopathies with eye involvement
- Skeletal abnormalities (delayed fontanelle closure, frontal bossing, femur/tibia bowing)
 - Hypophosphatemic rickets may develop with Fanconi syndrome
- Muscle cramps, spasms, weakness, paralysis
 - Can be seen in Gitelman syndrome due to hypomagnesemia
 - Hypokalemia may be seen in many tubular disorders and may cause weakness/paralysis particularly in the setting of local or general anesthetic use, pregnancy, and gastroenteritis.
- Gross hematuria, flank pain (stone symptoms)?
 - Associated with distal RTA
- Pregnancy history: history of polyhydramnios or oligohydramnios
 - Important in congenital conditions that may affect urine output of fetus
- Developmental history

- Some tubular diseases are associated with deafness, or cognitive impairments
- Delays can also occur if history of multiple episodes of dehydration

Thorough physical including:

- Hypotension
- Growth parameters
- Fair skin, blonde hair
- Dysmorphic features
- Rickets or bone deformities
- Hepatosplenomegaly

GENERAL INVESTIGATIONS

- Bloodwork
 - Kidney function
 - Blood gas and serum electrolytes - Is there a non-anion gap metabolic acidosis?
 - Serum extended electrolytes (calcium, magnesium, phosphate)
 - CBC – look for associated anemia associated with dRTA (elliptocytosis or spherocytosis)
- Urine Testing
 - Urinalysis and microscopy
 - What is the urine pH? Can be useful to differentiate between proximal and distal RTA
 - Urine that is not maximally acidified is seen in distal RTA and variable pH seen in proximal RTA due to distal acidification mechanism
 - Urine electrolytes
 - Calculate the urine anion gap ($U_{Na} + U_K - U_{Cl}$) – indicative of urine ammonium excretion (acid excretion). $Na + K < Cl$ means ammonium is likely present. $Na + K > Cl$ means that ammonium is likely absent and in the context of metabolic

acidosis this is inappropriate (?distal RTA)), Cannot be used in patient taking medications where there is an unmeasured anion or cation.

- Note: urine anion gap may not be useful if the urine is alkalotic (ie. pH >6.5), and in patients who are on medications excepting anything qualified as an alcohol or sugar (uncharged osmole) and in presence of ketones. In these cases, can calculate urine osmolal gap (measured osm- calculated osm), if >100 mosm/kg indicative of ammonium excretion.
- Also measure serum and urine phosphate if concerns for Fanconi syndrome (hypophosphatemia due to impaired phosphate reabsorption can be seen)
- Urine calcium-to-creatinine ratio
- Urine protein to creatinine ratio
- Urine amino acids
- Urine citrate (low due to proximal reabsorption in dRTA)
- Kidney ultrasounds
 - Useful to look for nephrocalcinosis associated with distal RTA and other tubular disorders
- Bone X-rays
 - If concerns for rickets

RENAL TUBULAR ACIDOSIS

Consider the following differential diagnosis:

Proximal renal tubular acidosis (RTA) (Type II)

- Defect in proximal bicarbonate reabsorption leading to non-anion gap metabolic acidosis
- Often associated with generalized proximal tubular dysfunction, AKA Fanconi syndrome, but can also be partial.
- Isolated proximal RTA often has a genetic etiology - rare
 - Inherited or sporadic mutations in transporters needed for normal tubular function
 - These may be autosomal recessive or dominant and can be associated with ocular abnormalities, short stature, enamel defects, hepatic involvement, cardiac involvement, intellectual impairment or occasionally basal ganglia calcifications

- Urine pH variable, negative urine anion gap (normal ammonium excretion)
- Diagnosis:
 - Based on presence of clinical and biochemical features (metabolic acidosis, urine pH, urine anion gap (to determine urine ammonium excretion))
 - Sodium bicarbonate load test: Follow urine pH while infusing sodium bicarbonate (as serum bicarbonate increases, the fractional excretion of bicarbonate will exceed normal of 15-20%). It is sometimes easier to check the serum bicarbonate when bicarbonaturia occurs (urine pH > 7.5) to show that the bicarb reabsorption threshold is < 24 mmol/L)
 - This test is not generally necessary to make the diagnosis in clinical practice.
- Management involves correction of acidosis with bicarbonate supplementation
 - Proximal typically requires much higher doses of bicarbonate than distal
- Fanconi Syndrome (more common presentation of proximal RTA)
 - Hereditary or acquired generalized proximal tubular dysfunction (Type II RTA plus additional tubular losses)
 - Features:
 - Low molecular weight proteinuria
 - Glucosuria
 - Phosphaturia
 - Aminoaciduria
 - Bicarbonaturia
 - Genetic etiologies (either inherited or sporadic mutations)
 - Cystinosis (most common): a lysosomal storage disease caused by a mutation in the CTNS gene resulting in impaired cysteine metabolism and cysteine accumulation in major organs
 - Lowe syndrome, Dent disease, Wilson disease, galactosemia, glycogen storage disease type 1, tyrosinemia, hereditary fructose intolerance
 - Acquired etiologies
 - Medications (ifosfamide, aminoglycosides, valproic acid, cisplatin), or any condition that causes profound phosphate depletion (eg. Diarrhea)
 - Diagnosis:

- Blood work with metabolic acidosis, hypophosphatemia, hyponatremia, hypokalemia, hypomagnesemia (not always all the features)
- Measure inappropriately high urinary excretion of glucose, phosphate, potassium, amino acids, tubular proteinuria, etc.
- For cystinosis measure blood leukocyte cysteine levels
- Ophthalmology to assess for cysteine crystals in the cornea in cystinosis or cataracts with galactosemia, lens irregularities with ORCL mutation in Dent's and Lowe's
- Thyroid function in cystinosis
- Management:
 - Correct all electrolyte abnormalities with appropriate supplementation
 - Cysteamine for cystinosis (eye drops and systemic treatment)

Distal RTA (Type I)

- Defect in distal urinary acid secretion resulting in non-anion gap metabolic acidosis
- Associated with hypokalemia, hyperchloremia, hypercalciuria, hypocitraturia
- Genetic etiology (inherited or sporadic)
 - Affects transporters in the intercalated cells of the distal tubule
- Acquired
 - Autoimmune diseases (mostly in adults)
 - Hypercalciuria (mostly in adults)
 - Medications (ifosfamide)
- Urine pH persistently greater than 5.5, positive urine anion gap (decreased ammonium excretion)
- Diagnosis:
 - Based on presence of clinical and biochemical findings discussed (metabolic acidosis, urine pH, urine anion gap (to determine urine ammonium excretion))
 - Nephrocalcinosis on renal ultrasound
- Management involves correction of acidosis with bicarbonate supplementation
 - Check for hearing loss or for RBC structural defects (elliptocytosis/spherocytosis)

Hyperkalemic RTA (Type IV)

- Hyperkalemic metabolic acidosis secondary to impaired aldosterone production or impaired renal responsiveness to aldosterone
- Aldosterone unresponsiveness can be inherited (pseudohypoaldosteronism) or a transient finding during episodes of acute pyelonephritis or urinary obstruction. Serum renin and aldosterone will be elevated
- Pseudohypoaldosteronism
 - Type I is either autosomal recessive or dominant (most common) and manifests in the neonatal period
 - AR: Mutations in the gene coding for the ENaC channel, shows systemic manifestations mimicking cystic fibrosis and tends to be the most severe form
 - AD: Mutations in the gene coding for the mineralocorticoid receptor, renal limited.
 - Type II features hypertension and hyperkalemia, but does not consistently have all the features of PHA
 - Type III transient forms of salt losing states caused by various etiologies (ie. UTI, obstructive uropathy)
- Diagnosis:
 - Based on clinical and biochemical features discussed
 - Genetic testing
- Management
 - Sodium supplementation (sodium chloride, sodium bicarbonate)
 - May need to consider potassium binding resins (ie. Kayexelate)

RTA Made Simple

If there's a normal anion gap metabolic acidosis, rule out a GI cause (diarrhea and high ileostomy output), and ensure no iatrogenic excess saline given to patient.

Also consider possibilities of the following:

- Hyperparathyroidism
- Bladder augments or bladder reconstructions

- Post-transplant ureteric leaks
- Posthypocapnea syndrome
- TPN prescribed without acetate
- Medications that impair bicarb absorption (topiramate, acetazolamide)) or H⁺ secretion (amiloride, spironolactone, trimethoprim, amphotericin, tacrolimus and cyclosporin, etc.)

If those aren't the cause, think RTA!

- In Type 1 (distal) the potassium is low/normal (because '1' is low)
- In Type 4 the potassium is high (because '4' is high)
- In Type 2 (proximal) they are losing '2' many things (because there's typically a Fanconi syndrome)

TUBULAR TRANSPORT DISORDERS

Bartter Syndromes

- Autosomal recessive (usually) defect in tubular electrolyte transporters resulting in hypokalemic metabolic alkalosis and urinary loss of sodium chloride (salt wasting)
 - Typically discovered due to hypochloremic hypokalemic metabolic alkalosis in a neonate/child with dehydration or related to growth concerns
 - Other common features may include hypercalciuria, elevated renin and aldosterone (although these tests may take much longer to be resulted)
 - Affected transporters include ROMK (most common), and NKCC2
- Five types depending on involved mutations and associated clinical presentation
 - Type I
 - Type II
 - Type III
 - Type IV
 - Type V (the only autosomal dominant type)
- Diagnosis:
 - Based on the presence of clinical and biochemical findings discussed

- Use urine electrolyte measurements to support the diagnosis
- Genetic testing to confirm mutation and subtype
- Management:
 - Electrolyte correction with supplementation (potassium chloride usually at high doses is required, high sodium diet or sodium supplementation)
 - May use NSAIDs to reduce urine output
 - Counselling to prevent episodes of dehydration
 - Monitoring of hypercalciuria and nephrocalcinosis
 - Long term monitoring for growth, and development of chronic kidney disease is required

Gitelman Syndrome

- Autosomal recessive defect in tubule electrolyte transporters, most commonly the thiazide sensitive sodium chloride co-transporter, resulting in hypochloremic hypokalemic metabolic alkalosis
 - Also involves hypomagnesemia and hypocalciuria (different from Bartters)
 - Typically presents in later childhood or adulthood with episodes of severe dehydration, muscle cramps (due to hypomagnesemia), fatigue, polyuria
- Diagnosis:
 - Based on the presence of clinical and biochemical findings discussed
 - Genetic testing to confirm mutation in transporter
- Management:
 - Electrolyte correction with supplementation (typically potassium and magnesium)

NEPHROGENIC DIABETES INSIPIDUS

- Defect in response to anti-diuretic hormone (ADH) causing inappropriate water loss (increased collecting tubule permeability to free water) and hyponatremia
- Inherited or acquired forms
 - Inherited forms are commonly X-linked recessive but can also be autosomal recessive or dominant

- Acquired causes are variable and include obstructive uropathy, renal cystic disease, interstitial nephritis, nephrocalcinosis
- Inherited forms present during neonatal period with polyuria and hypernatremia
- Diagnosis:
 - Urine osmolality of <290 mOsm/kg with a serum osmolality ≥ 290 mOsm/kg followed by lack of response to vasopressin (see below) is diagnostic
 - If these criteria are not met but nephrogenic DI is being considered, a formal water deprivation test can be done
 - Withhold fluids and periodically measure urine and serum osmolality until the serum osmolality is > 290 mOsm/kg then administer vasopressin
 - Consider stopping the test early if the body weight decreases by $>3\%$
 - Administer vasopressin then monitor urine and serum osmolality every 4 hours, if there is no response (no change in osmolality) this suggests a diagnosis of nephrogenic DI
- Management:
 - In acute situations, rehydrate with hypotonic solutions (IV or enteral)
 - Patients require adequate access to free water
 - G-tube may need to be considered for infants
 - Low osmolar, low sodium diet
 - Decreases urine output by reducing the solute load
 - Thiazide diuretics (+/- potassium sparing diuretics)
 - Increases proximal sodium and water absorption as an adaptive response to the initial diuresis
 - Indomethacin
 - May be needed to reduce water losses

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16. URINARY TRACT INFECTIONS AND VESICoureTERAL REFLUX

OVERVIEW

UTI Prevalence

Note: Seven percent of infant and children presenting with fever (even without symptoms) are diagnosed with urinary tract infection.

Risk Factors

- Sex
 - Males > Females in infancy
 - Females > Males in childhood
- Vesicoureteral reflux
- Neurogenic bladder
- Phimosis (Uncircumcised boys (20% prevalence compared to around 2.5% in circumcised))
- Anatomical abnormalities of the urinary tract
- Constipation
- Holding maneuvers

Symptoms

In newborns and young infants, fever and irritability may be the only symptoms. Other symptoms include:

- Hematuria
- Cloudy / foul smelling urine
- Dysuria
- Frequency
- Lower abdominal pain
- Secondary enuresis

- Vomiting, diarrhea

Urine Collection Methods

- Clean catch with surrounding area adequately cleaned
- Mid-stream urine sample in toilet trained children
- Bag sample – 63% chance of contamination
Can be used as a screen (urinalysis) but should not be sent for culture
- Urinary catheterization
- Suprapubic aspiration

*Urine collection must occur before starting antibiotics because a single dose of an effective antibiotic can rapidly sterilize the urine.

INVESTIGATIONS

Urinalysis, urine culture

- Presence of nitrites, leucocyte esterase and white blood cells are suggestive of presence of infection.
- Bacteria & yeast seen on microscopic urinalysis are often contaminants.

Bloodwork

- CBC
- CRP
- Urea, creatinine and serum electrolytes; If suspected pyelonephritis or use of nephrotoxic antibiotics

* Blood cultures should only be performed if child is unwell and systemic infection is considered or in infants where risk of urosepsis is high.

Imaging

Diagnostic imaging in children with febrile UTI are used to identify whether severe vesicoureteral reflux (VUR) or structural anomalies are present. Antibiotic prophylaxis pending results of imaging is no longer advised routinely.

- Renal and bladder US in children <2 years of age after their first febrile UTI to detect hydronephrosis that may suggest underlying VUR.
 - Ultrasound cannot be used to diagnose VUR. Note that the degree of hydronephrosis does not always correlate with the severity of the reflux.
- VCUG: The CPS recommends VCUG for children with first UTI and RBUS suggesting underlying renal anatomical abnormalities or hydronephrosis, scarring or other findings that may suggest underlying reflux/obstructive uropathy or children < 2 years with a second documented UTI.
 - Optimal diagnostic imaging to diagnose VUR and identify anatomy of male urethra however not first line due to invasive nature of procedure, exposure to radiation and risk of introduction of infection.
- Dimercaptosuccinic acid (DMSA): can be used to diagnose pyelonephritis acutely or assess renal scarring months later when the diagnosis of acute or recurrent UTI, respectively, is in doubt. Associated with more radiation exposure.

UTI TREATMENT

Common Pathogens

- *Escherichia coli*
- *Klebsiella pneumonia*
- *Enterobacter* species
- *Citrobacter* species
- *Serratia* species
- *Staphylococcus saprophyticus* (adolescent females)

*Mixed growth or growth of other organisms usually indicates that the urine is contaminated.

Treatment

- May start empiric antibiotics pending urine culture results (often cephalexin, trimethoprim-sulfamethoxazole, or amoxicillin).
- Studies showed no difference between oral vs parenteral antibiotics. Duration of treatment varies between 7-14 days depending on clinical scenario.

- Please see CPS position statement: Urinary tract infections in infants and children: Diagnosis and management, Table 3 for list of common antimicrobials used for empiric treatment and dosage.

VESICoureTERAL REFLUX

- Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract.
- **Primary VUR** – Reflux due to incompetent or inadequate closure of the ureterovesical junction (UVJ).
- **Secondary VUR** – Reflux as a result of abnormally high voiding pressure in the bladder that results in failure of the closure of the UVJ during bladder contraction.
 - This is usually the result of bladder bowel dysfunction, neurogenic bladder and posterior urethral valves

Epidemiology

- Primary VUR is the most common urologic finding in children, occurring in approximately 1 percent of newborns.

Presentation

- VUR may be suspected antenatally when evidence of hydronephrosis is seen. Postnatally an episode of febrile UTI can lead to workup revealing VUR.

Diagnosis

- Diagnosis of presence and degree of reflux can be determined by voiding cystourethrogram (VCUG) or radionuclide cystogram*.
- *Radionuclide cystogram - Does not reliably show bladder wall appearance, grade I reflux or urethral anatomy in boys.

Grading

- Grade I – Reflux only fills the ureter without dilation.
- Grade II – Reflux fills the ureter and the collecting system without dilation

- Grade III – Reflux fills and mildly dilates the ureter and the collecting system with mild blunting of the calices.
- Grade IV – Reflux fills and grossly dilates the ureter and the collecting system with blunting of the calices. Some tortuosity of the ureter is also present.
- Grade V – Massive reflux grossly dilates the collecting system. All the calices are blunted with a loss of papillary impression, and intrarenal reflux may be present. There is significant ureteral dilation and tortuosity.

Prophylactic antibiotic recommendations

- When a child presents with grade IV or V reflux, or significant anomalies prophylactic antibiotics are considered (e.g. grade III VUR in solitary kidney)
- Trimethoprim/Sulfamethoxazole, Nitrofurantoin or Cephalexin are the usual choices for prophylaxis. Antibiotics are generally used for 3-6 months then reassessed. Prophylaxis should be stopped if patient develops UTI with an organism that is resistant to the antibiotic.

ENURESIS

- **Primary enuresis (enuresis is at night):** Primary enuresis is defined as nocturnal wetting in a child older than 5 years of age who has never been dry on consecutive nights for longer than 6 months.
- **Secondary enuresis:** Resumption of enuresis after at least six months of urinary continence
- **Daytime wetting:** Urinary incontinence that occurs while the child is awake.

Causes of primary enuresis

- Nocturnal polyuria
- Detrusor instability
- Decreased functional bladder capacity
- Delay in CNS maturation
- Global developmental delay

Causes of secondary enuresis

- Bladder dysfunction
- Constipation
- Diabetes insipidus
- Diabetes mellitus
- Urinary tract infection
- Psychological stress

Investigations

- Focused history & physical exam is key. Urinalysis and culture are non-invasive important tools to rule out some medical causes of enuresis.
- Renal and bladder ultrasound is usually performed as part of work up. Other Imaging modalities to rule out specific underlying causes depending on clinical scenario including daytime enuresis may include:
 - Post-voiding bladder scan (to look at bladder emptying)
 - VCUG
 - MRI of lumbosacral spine
 - Urodynamic studies

Management

- Management of enuresis depends on underlying cause, patient age and other associated factors.
- Education, addressing daytime symptoms, motivational therapy and bladder training.
- Other non-pharmacological management includes enuresis alarms however sleep disruption is a side effect.
- Treatment is considered successful when the child achieves continence for 14 consecutive nights within a 16-week period

Pharmacologic therapy

- Anticholinergics (e.g., oxybutynin) decrease detrusor tone, frequency, and urgency and improve bladder capacity. Useful in patients with combined daytime wetting and enuresis.

Use with caution in patient with bladder dysfunction (PUV) as they may not empty the bladder properly with potential secondary high pressure to kidneys.

- Desmopressin therapy is combined with fluid restriction (on nights when the drug is administered) and voiding before bedtime. Combining desmopressin therapy with an enuresis alarm improves the response rate and reduces relapse.
- Tricyclic antidepressants reduce bed-wetting by one wet night per week during treatment.

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