

Chapter 19

Nephrology

Paul M. Gallo, MD, PhD

I. URINALYSIS¹: TABLE 19.1

- A. Common indications include: Infectious workup (urinary tract infection [UTI], pyelonephritis), abdominal trauma, suspected diabetes or renal disease, rhabdomyolysis, edema, failure to thrive.
- B. Best if urine specimen is evaluated within 1 hour of voiding, otherwise should be kept at 4°C.
- C. Annual screening UAs are not recommended by the American Academy of Pediatrics (AAP) unless patient is at high risk of chronic kidney disease.

II. KIDNEY FUNCTION TESTS

A. Tests of Glomerular Function

- 1. **Glomerulogenesis is complete at 36 weeks gestation.** Glomerular filtration rate (GFR) increases over the first two years of life related to glomerular maturation.
- 2. **Normal GFR values**, as measured by inulin clearance (gold standard), are shown in [Table 19.2](#).
- 3. **Creatinine clearance (CCr):**
Closely approximates inulin clearance in the normal range of GFR. When GFR is low, CCr overestimates GFR. May be inaccurate in children with obstructive uropathy or problems with bladder emptying secondary to challenges getting complete timed urine collections.

$$CCr \text{ (mL/min / } 1.73 \text{ m}^2\text{)} = [U \times (V/P)] \times 1.73 / BSA,$$

where U (mg/dL) = urinary creatinine concentration; V (mL/min) = total urine volume (mL) divided by the duration of the collection (min) (24 hours = 1440 minutes); P (mg/dL) = serum creatinine concentration (may average two levels); and BSA (m^2) = body surface area.

- 4. **Estimated GFR (eGFR) from plasma creatinine:** Varies related to body size/muscle mass. If body habitus is markedly abnormal or a precise measurement of GFR is needed, consider other methods. Creatinine must be in steady state to estimate GFR; use caution in the setting of acute kidney injury. Three methods to calculate estimated GFR:

TABLE 19.1
URINALYSIS COMPONENTS

Test	Purpose	Normal Findings	Special Notes
Appearance	General impression	Colorless to amber. Cloudy/turbid urine can be normal.	Causes of turbid urine: <ul style="list-style-type: none">• Uric acid crystals in acidic urine• Phosphate crystals in alkaline urine• Cellular and infectious material Causes of red/orange urine: Foods, drugs (propofol, chlorpromazine, thioridazine, rifampin), hemoglobinuria, porphyrias
Specific Gravity	Correlates with kidney's ability to concentrate urine; surrogate of osmolality and hydration status	Between 1.003 and 1.030	Isosthenuria: Urine with osmolality equal to plasma (specific gravity of 1.010). May indicate disease affecting ability to concentrate/dilute urine. Falsely elevated by: Glucose, high protein, iodine-based contrast, ketoacids
pH	Evaluate renal tubule hydrogen ion maintenance	pH 4.5–8, average range of 5–6	Influenced by serum pH Alkaline urine may indicate UTI with urea-splitting organisms or certain types of stones
Protein	Evaluate for proteinuria	Dipstick values: Negative Trace 1+ (~30 mg/dL) 2+ (~100 mg/dL) 3+ (~300 mg/dL) 4+ (>1000 mg/dL)	Confirm and quantify significant proteinuria with random urine protein/creatinine ratio or 24-hr urine collection Evaluate for postural proteinuria with first morning void Concentrated urine can lead to false positive result
Glucose	Detect glucose in urine	Glcosuria is always abnormal	Glcosuria typically seen when blood glucose >160–180 mg/dL Consider diabetes mellitus, proximal renal tubular disease, pregnancy Dipstick only measures glucose; reduction tests (Clinitest) will detect other sugars for suspected inborn errors of metabolism
Ketones	Detect breakdown of fatty acids	Negative to trace	Suggests diabetes mellitus or starvation-induced catabolism Neonatal ketoacidosis may indicate inborn error of metabolism
Nitrite	Detect gram-negative bacterial metabolism	Negative	Specific (90%–100%), but not sensitive (15%–82%) for UTI False positive from phenazopyridine

Test	Purpose	Normal Findings	Special Notes
Leukocyte Esterase	Detect presence of WBCs	Negative	Indicates pyuria Sensitive (67%–84%), but less specific (64%–92%) for UTI
Hemoglobin	Detects presence of RBCs or hemoglobin	Negative	Indicates hematuria or hemoglobinuria False positive on dipstick: Myoglobin (crush injury, rhabdomyolysis, vigorous exercise, etc.), contamination with blood outside the urinary tract
Bilirubin, Urobilinogen	Evaluate for hyperbilirubinemia	Negative	Positive with indirect hyperbilirubinemia Urobilinogen may be present in low amounts; increased in all cases of hyperbilirubinemia
Red Blood Cells	Differentiate hemoglobinuria from intact RBCs	Centrifuged urine normally contains <5 RBC/hpf	RBC morphology suggest location of bleeding; dysmorphic RBCs suggest a glomerular origin, normal RBCs suggest lower tract bleeding
White Blood Cells	Detect inflammation/infection	Centrifuged urine normally contains <5 WBC/hpf	Consider UTI, sterile pyuria, inflammatory disorders (e.g., Kawasaki)
Epithelial Cells	Index of possible contamination	<5 squamous epithelial cells/hpf	15–20 squamous epithelial cells/hpf suggests contamination, although any amount may indicate contamination
Sediment	Investigate for formed elements: casts, cells, crystals	None	Hyaline casts: may be normal (e.g., dehydration)

RBC, Red blood cell; UTI, urinary tract infection; WBC, white blood cell

TABLE 19.2
NORMAL VALUES OF GLOMERULAR FILTRATION RATE

Age (Sex)	Mean GFR \pm SD (mL/min/1.73 m ²)
1 week (M and F)	41 \pm 15
2–8 weeks (M and F)	66 \pm 25
>8 weeks (M and F)	96 \pm 22
2–12 years (M and F)	133 \pm 27
13–21 years (M)	140 \pm 30
13–21 years (F)	126 \pm 22

F, Female; M, male; SD, standard deviation.

Adapted from: Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children and Adolescents: Evaluation, Classification, and Stratification. *Pediatrics*. 2003;111:1416.

TABLE 19.3**PROPORTIONALITY CONSTANT FOR CALCULATING GLOMERULAR FILTRATION RATE**

Age	<i>k</i> -Values
Low birth weight during first year of life	0.33
Term AGA during first year of life	0.45
Children and adolescent girls	0.55
Adolescent boys	0.70

AGA, Appropriate for gestational age.

Data from Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am.* 1987;34:571.

- a. **Bedside Chronic Kidney Disease in Children (CKiD) cohort:** Only applicable if creatinine measured by enzymatic assay. Recommended for eGFR determination in children aged 1 to 16 years. Estimated GFRs of ≥ 75 mL/min/1.73 m² determined by this equation likely represent normal kidney function; clinical correlation is recommended with GFR estimation.²

$$\text{eGFR}(\text{mL/min}/1.73 \text{ m}^2) = 0.413 \times (\text{L}/\text{Pcr}),$$

where 0.413 is the proportionality constant, *L* = height (cm), and *Pcr* = plasma creatinine (mg/dL).

- b. **Schwartz equation:** Historical equation for eGFR in children. However, laboratories are increasingly shifting to enzymatic assays to determine creatinine; use of enzymatically determined creatinine (vs Jaffe method) with the Schwartz equation leads to overestimation of GFR and should be considered when applying clinically:

$$\text{eGFR}(\text{mL/min}/1.73 \text{ m}^2) = kL/\text{Pcr},$$

where *k* = proportionality constant (Table 19.3); *L* = height (cm); and *Pcr* = plasma creatinine (mg/dL).

- c. **Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):** Used to calculate GFR in those >18 years old. Available at NKDEP website (see Section XII).
- 5. **Other measurements of GFR:** May be used when more precise determination of GFR is needed (e.g., dosing of chemotherapy). These methods include iothalamate, DTPA, and iohexol. Cystatin C is a low molecular protein that can also be used to estimate GFR and is more accurate than serum creatinine in individuals with conditions that significantly impact muscle mass, the source of creatinine.

B. Tests of Kidney Tubular Function

1. Proximal tubule and solute handling:

- a. **Proximal tubule reabsorption:** Proximal tubule is responsible for reabsorption of electrolytes, glucose, and amino acids. Studies to evaluate

proximal tubular function compare urine and blood levels of specific compounds, arriving at a percentage of tubular reabsorption (Tx):

$$Tx = 1 - [(Ux / Px) / (UCr / PCr)] \times 100\%,$$

where Ux = concentration of compound in urine; Px = concentration of compound in plasma; Ucr = concentration of creatinine in urine; and Pcr = concentration of creatinine in plasma. This formula can be used for amino acids, electrolytes, calcium, and phosphorus. It is commonly used to calculate tubular reabsorption of phosphate (TRP). In a patient with hypophosphatemia and preserved proximal tubular function, the tubular reabsorption of phosphate would be expected to be near 100%.

- b. **Fractional excretion of sodium (FENa)**³: Commonly used to assess tubular function. Must consider sodium and volume status. May be inaccurate with recent diuretic use.

$$FENa = [(UNa / PNa) / (UCr / PCr)] \times 100\%,$$

where UNa = concentration of sodium in urine; and PNa = concentration of sodium in plasma. FENa is usually <1% in prerenal azotemia or glomerulonephritis, and >1% (usually >3%) in acute tubular necrosis (ATN) or postrenal azotemia. Infants have diminished ability to reabsorb sodium; FENa in volume-depleted infants is <3%.

- c. **Fractional excretion of urea (FEurea)**: May be useful in certain clinical scenarios, including patients on diuretics. Use FENa equation above, substituting urea for sodium. FEurea is usually <35% in prerenal azotemia and >50% in ATN.³
- d. **Fractional excretion of bicarbonate (FEHCO₃)**: May help differentiate the types of renal tubular acidosis (RTA). The majority of bicarb reabsorption occurs in proximal tubule.

$$FEHCO_3 = [(UHCO_3 / PHCO_3) / (UCr / PCr)] \times 100\%,$$

Normal FEHCO₃ is <5%. Distal RTA is usually <5%. >15% suggests proximal (Type II) RTA.

2. Distal tubule and pH balance:

- a. **Urine anion gap (UAG)**: Used as an indirect measure of ammonium production in the distal nephron.

$$UAG = UNa + UK - UCl,$$

where UNa = concentration of sodium in urine; UK = concentration of potassium in urine; and UCl = concentration of chloride in urine. Positive UAG (usually >20) suggests a distal RTA. Negative UAG (usually <-20) suggests high urinary NH₄⁺ (e.g., secondary to diarrhea).

- b. **Urine pH**: A urine acidification defect (distal RTA) should be suspected when random urine pH values are >6 in the presence of moderate systemic metabolic acidosis. Confirm acidification defects by simultaneous venous or arterial pH, plasma bicarbonate concentration, and determination of the pH of fresh urine.
- c. **Urine osmolality**: Urine is concentrated distally in the kidney tubules. Urine osmolality, ideally on a first morning urine specimen, may be

TABLE 19.4
AGE-ADJUSTED CALCIUM/CREATININE RATIOS

Age	Ca ²⁺ /Cr Ratio (mg/mg) (95th Percentile for Age)
<7 months	0.86
7–18 months	0.60
19 months to 6 years	0.42
Adults	0.22

From Sargent JD, Stukel TA, Kresel J, et al. Normal values for random urinary calcium-to-creatinine ratios in infancy. *J Pediatr.* 1993;123:393.

used to evaluate capacity to concentrate urine. If osmolality is >600 mOsm/L, then tubular dysfunction, including disease states such as diabetes insipidus leading to inappropriate water loss, is unlikely. For more formal testing, see the water deprivation test in Chapter 10.

- d. **Urine calcium:** Hypercalciuria may be seen with distal RTA, vitamin D intoxication, hyperparathyroidism, immobilization, excessive calcium intake, use of steroids or loop diuretics, or an idiopathic cause.

Diagnosis is as follows:

- (1). 24-hour urine: Calcium >4 mg/kg/24 hr (gold standard)
- (2). Spot urine: Determine calcium/creatinine (Ca/Cr) ratio. Normal urine Ca/Cr ratio does not rule out hypercalciuria. Correlate clinically and follow elevated spot urine Ca/Cr ratio with a 24-hr urine calcium determination if indicated (Table 19.4).⁴

III. CHRONIC HYPERTENSION⁵⁻⁷

Note: See Chapter 1 for the management of acute hypertension and Chapter 7 for normal blood pressure (BP) parameters.

A. Definition

Hypertension is defined as the sustained elevation of BP at or above the 95th percentile for those <13 years or ≥130/80 for those ≥13 years. Any BP that is >90th percentile or ≥120/80 should be repeated at a clinic visit; if persistently elevated when confirmed by manual auscultation, the child should return for a repeat measurement for confirmation (see Section III.E).

B. Measurement of Blood Pressure in Children

1. All children ≥3 years should have BP measured annually. Children ≥3 years should have BP measured at **all** visits if at increased risk for hypertension: obesity, taking medications known to increase BP, renal disease, history of aortic arch obstruction/coarctation, diabetes.
2. Children aged <3 years with risk factors should have BP measured at all well-child care visits. Risk factors include history of prematurity <32 weeks gestation or small for gestational age, very low birth weight, congenital heart disease, kidney/urologic disease or family history of

TABLE 19.5**CAUSES OF HYPERTENSION BY AGE GROUP**

Age	Most Common	Less Common
Neonates/infants	Renal artery thrombosis after umbilical artery catheterization	Bronchopulmonary dysplasia Medications
	Coarctation of aorta	Patent ductus arteriosus
	Renal artery stenosis	Intraventricular hemorrhage
1–10 years	Renal parenchymal disease Coarctation of aorta	Renal artery stenosis Hypercalcemia Neurofibromatosis Neurogenic tumors Pheochromocytoma Mineralocorticoid excess Hyperthyroidism Transient hypertension Immobilization-induced Sleep apnea Essential hypertension Medications
11 years to adolescence	Renal parenchymal disease Essential hypertension	All diagnoses listed in this table

Modified from Sinaiko A. Hypertension in children. *N Engl J Med.* 1996;335:26.

kidney disease, recurrent UTIs, malignancy, solid organ or bone marrow transplant, taking medications known to increase BP, systemic illness associated with hypertension, and evidence of increased intracranial pressure.

- BP should be measured in a seated position in an upper extremity after 5 minutes of rest with feet/back/arm supported and mid-cuff at heart level; auscultation is preferred. Appropriate cuff size has a bladder width at least 40% of upper arm circumference at midway point. Bladder length should cover 80% to 100% of arm circumference. Cuffs that are too small may result in falsely elevated BPs. Choose a larger-sized cuff if there is a choice between two.

C. Etiologies of Hypertension in Neonates, Infants, and Children **(Table 19.5)**

Drugs causing hypertension include glucocorticoids, calcineurin inhibitors, sympathomimetics, oral contraceptives, stimulants (methylphenidate), ephedrine, erythropoietin, NSAIDs, caffeine, tobacco, ethanol, cocaine, amphetamines.

D. Evaluation of Chronic Hypertension

- Rule out factitious causes of hypertension (improper cuff size or measurement technique [e.g., manual vs. oscillometric]), non-pathologic causes of hypertension (e.g., fever, pain, anxiety, muscle spasm), and iatrogenic mechanisms (e.g., medications, excessive fluid administration).

2. **History:** Headache, blurred vision, dyspnea on exertion, edema, obstructive sleep apnea symptoms (including poor sleep quality or duration), endocrine symptoms (diaphoresis, flushing, constipation, weakness, etc.), history of neonatal intensive care unit stay, rule out pregnancy, history of UTIs, history of medications and supplements, illicit drug use, or any family history of kidney dysfunction or hypertension.
3. **Physical examination:** Four-extremity pulses and BPs, endocrine disease stigmata, edema, hypertrophied tonsils, skin lesions, abdominal mass, or abdominal bruit.
4. **Clinical evaluation of confirmed hypertension:**
 - a. Laboratory studies:
 - (1) All patients: Urinalysis (UA), serum electrolytes, creatinine, blood urea nitrogen (BUN), lipid profile
 - (2) Obese patients: Hgb A1c, AST/ALT, fasting lipid panel
 - (3) Consider on basis of history and exam: Fasting serum glucose, thyroid stimulating hormone, drug screen, polysomnography, complete blood count
 - b. Clinical practice guidelines recommend 24-hour ambulatory blood pressure monitoring (ABPM) be conducted in all children with persistently elevated blood pressure to confirm the diagnosis of hypertension. Other at-risk populations (e.g., coarctation of the aorta status-post repair, CKD, history of hypertension) should also have this monitoring done yearly regardless of clinic blood pressure.
 - c. Imaging:
 - (1) Renal ultrasound in patients <6 years old or those with abnormal UA or renal function.
 - (2) Echocardiography to evaluate for left ventricular hypertrophy if pharmacologic treatment considered.
 - (3) Consider renovascular imaging if renal artery stenosis is suspected.
 - d. Patients ≥6 years of age do not require extensive evaluation for secondary causes if they have a strong family history of hypertension (HTN), are overweight, and do not have any evidence of secondary causes on history and physical exam.

E. Classification and Treatment of Hypertension (Table 19.6)

Target: SBP and DBP to <90th percentile and <130/80 mmHg in adolescents ≥13 years old. Consider target 50th percentile in those with CKD.

1. **Nonpharmacologic:** Aerobic exercise, sodium restriction, smoking cessation, and weight loss indicated in all patients with hypertension. Reevaluate BP after lifestyle interventions, and begin pharmacologic therapy if hypertension persists.
2. **Pharmacologic:** Indications include secondary hypertension, symptomatic hypertension, stage 2 hypertension without a clearly modifiable factor (e.g., obesity), diabetes mellitus, and persistent hypertension despite nonpharmacologic measures.

TABLE 19.6**CLASSIFICATION OF HYPERTENSION IN CHILDREN AND ADOLESCENTS AND MANAGEMENT RECOMMENDATIONS**

	Ages 1–13 Years	Ages \geq13 Years	Frequency of BP Measurement	Pharmacologic Therapy (in Addition to Lifestyle Modifications)
Normal BP	<90th percentile	<120/ $<$ 80	Annually (or sooner if at increased risk; see Section III.B)	None
Elevated BP	90th to <95th percentile <i>OR</i> 120/80 to <95th percentile, whichever is lower	120/ $<$ 80 to 129/ $<$ 80 <i>OR</i> 130/80 to 139/89, whichever is lower	Recheck in 6 months; if persistent over 2 additional visits, conduct ABPM and diagnostic evaluation	None, unless compelling indications: CKD, DM
Stage 1 Hypertension	95th to 95th percentile plus 12 mmHg <i>OR</i> 130/80 to 139/89, whichever is lower	130/80 to 139/89	Recheck in 1–2 weeks; if persistently elevated over 2 additional visits, conduct ABPM and diagnostic evaluation	Initiate therapy, especially if symptomatic, end-organ damage is present, CKD, DM, persistent hypertension despite nonpharmacologic measures
Stage 2 Hypertension	\geq 95th percentile plus 12 mmHg <i>OR</i> \geq 140/90, whichever is lower	\geq 140/90	Evaluate and refer within 1 week, or immediately if the patient is symptomatic	Initiate therapy

All blood pressures expressed in mmHg.

ABPM, Ambulatory blood pressure monitoring; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure.

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

3. **Treatment monitoring:** Repeat echocardiogram every 6 to 12 months in those with cardiac end organ damage or those at high risk. Repeated 24-hour ABPM can be used to assess treatment effectiveness as needed.

F. Antihypertensive Drugs for Outpatient Management of Primary Hypertension in Children 1 to 17 Years of Age

Clinical guidelines recommend angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, thiazide diuretics, or long-acting calcium channel blockers as first-line medications for management of chronic hypertension in children.⁶ Medication choice may be impacted by underlying comorbidities, contraindications, and side effects. Providers should familiarize themselves with existing guidelines, medication contraindications, and side effects. A list of medications and common side effects is found in Table 19.7.

TABLE 19.7

ANTIHYPERTENSIVE DRUGS FOR OUTPATIENT MANAGEMENT OF HYPERTENSION IN CHILDREN 1–17 YEARS OF AGE

Class	Drug	Comments
Angiotensin-converting enzyme (ACE) inhibitor	Benazepril	Blocks conversion of angiotensin I to angiotensin II
	Captopril	Decreases proteinuria while preserving renal function
	Enalapril	Contraindicated: Pregnancy, compromised renal perfusion (e.g., renal artery stenosis)
	Fosinopril	Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia
	Lisinopril	
	Ramipril	
Angiotensin-II receptor blocker (ARB)	Quinapril	Monitor for cough and angioedema
	Candesartan	Contraindicated: Pregnancy
	Irbesartan	Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia
	Losartan	
	Olmesartan	
α - and β -Blockers	Valsartan	
	Labetalol	Cause decreased peripheral resistance and decreased heart rate
	Carvedilol	Contraindications: Asthma, heart failure, insulin-dependent diabetes Heart rate is dose-limiting May impair athletic performance
β -Blocker	Atenolol	Decreases heart rate, cardiac output, and renin release
	Esmolol	Noncardioselective agents (e.g., propranolol) are contraindicated in asthma and heart failure
	Metoprolol	Metoprolol and atenolol are β_1 selective
	Propranolol	Heart rate is dose-limiting May impair athletic performance
		Should not be used in insulin-dependent diabetics
Calcium channel blocker	Amlodipine	Acts on vascular smooth muscles
	Felodipine	Renal perfusion/function is minimally affected; generally few side effects
	Isradipine	Amlodipine and isradipine can be compounded into suspensions
Extended-release nifedipine		May cause tachycardia
	nifedipine	

Class	Drug	Comments
Central α-agonist	Clonidine	Stimulates brainstem α_2 receptors and decreases peripheral adrenergic drive May cause dry mouth and/or sedation (↓ opiate withdrawal) Transdermal preparation also available Sudden cessation of therapy can lead to severe rebound hypertension
Loop diuretics	Furosemide Bumetanide	Side effects are hyponatremia, hypokalemia, and ototoxicity
Thiazide diuretics	Hydrochlorothiazide Chlorthalidone Chlorothiazide	Side effects are hypokalemia, hypercalcemia, hyperuricemia, and hyperlipidemia
Potassium-sparing diuretics	Spironolactone Triamterene Amiloride	Useful as add-on therapy in patients being treated with drugs from other drug classes Potassium-sparing diuretics are modest antihypertensives. They may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB
Peripheral α-antagonist	Doxazosin Prazosin Terazosin	May cause hypotension and syncope, especially after first dose
Vasodilator	Hydralazine Minoxidil	Directly acts on vascular smooth muscle and is very potent Tachycardia, sodium retention, and water retention are common side effects Used in combination with diuretics or β-blockers Minoxidil is usually reserved for patients with hypertension resistant to multiple drugs

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

IV. URINARY TRACT INFECTIONS⁸⁻¹³

A. History

Highly dependent on patient age. Inquire about fever, dysuria, frequency, urgency, and back/abdominal pain. Obtain voiding history (stool, urine), stream characteristics in toilet-trained children, sexual activity, sexual abuse, circumcision status, prolonged/bubble baths or swimming, evaluation of growth curve, recent antibiotic use, and family history of vesicoureteral reflux (VUR), recurrent UTIs, or chronic kidney disease.

B. Physical Examination

Vital signs, abdominal examination for tenderness, flank masses, bowel distention, evidence of impaction, meatal stenosis or circumcision in males, vulvovaginitis or labial adhesions in females, neurologic examination of lower extremities, perineal sensation and reflexes, and rectal and sacral examination (for anteriorly placed anus).

C. Risk Factors

2011 AAP guidelines,⁸ reaffirmed in 2016,⁹ for children 2 to 24 months provide resources to help clinicians stratify the risk of UTI in the absence of another source of infection in a febrile child.

1. Females are at higher risk for UTI than males.
2. Uncircumcised males are at higher risk than circumcised males.
3. Other risk factors include non-black race, fever $\geq 39^{\circ}\text{C}$, and fever >1 to 2 days.

D. Methods of Urine Collection

1. **If a child is 2 months to 2 years old, has a fever, and appears sufficiently ill to warrant immediate antibiotics**, obtain UA and urine culture by transurethral catheterization. **Suprapubic percutaneous aspiration** may be useful in critically ill children, is generally very safe, and is similar to bladder catheterization in sensitivity and specificity.
2. **If a child is 2 months to 2 years old, has a fever, and does not appear ill enough to warrant immediate antibiotics**, obtain urine by catheterization or the most convenient method available. **Bag or absorbent pad** may be helpful when UTI is unlikely (to rule out infection), but both have very high false positive rates ($>75\%$ of cultures positive) and should not be sent for culture.⁸ If UA does not suggest UTI, it is reasonable to avoid antimicrobial therapy. If UA does suggest UTI, urine culture should be obtained by catheterization.
3. **If a child is >2 years old and toilet trained**, may provide midstream clean-catch urine specimen.

E. Diagnosis

To establish the diagnosis of UTI, both UA results suggestive of infection and positive urine culture are recommended.

1. Nitrite test:
 - a. Detects products of reduction of dietary nitrates by urinary gram-negative bacterial species (especially *Escherichia coli*, *Klebsiella*, and *Proteus*).
 - b. Sensitivity 15% to 82% and specificity 90% to 100% for UTI.⁸
 - c. Special circumstances: False-negative (low sensitivity) results commonly occur with insufficient time (<4 hours) for conversion of urinary nitrates to nitrites (age-dependent voiding frequency) and inability of bacteria to reduce nitrates to nitrites (many gram-positive organisms such as *Enterococcus*, *Mycobacterium* spp., and fungi).
2. Leukocyte esterase test:
 - a. Detects esterase released from leukocyte lysis.
 - b. Sensitivity 67% to 84% and specificity 64% to 92% for UTI.⁸
3. Pyuria is defined at a threshold of ≥ 5 WBCs/hpf. Absence of pyuria is rare if a true UTI is present.
4. Urine culture:
 - a. Transurethral catheterization or suprapubic aspiration: $>50,000$ colony-forming units (CFU) per mL diagnostic of UTI. Some sources suggest $>10,000$ CFU/mL in the presence of fever, symptoms, and pyuria may also be diagnostic.¹⁰

- b. Clean catch: >100,000 CFU/mL necessary to diagnose a UTI.
- c. Bagged specimen: Should not be used to collect urine culture.
- d. Catheter-associated (indwelling urethral or suprapubic): No specific data for pediatric patients. Adult Infectious Diseases Society of America guidelines define it as presence of symptoms and signs compatible with UTI and >1000 CFU/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose catheter has been removed within previous 48 hours.¹¹

F. Classification

Pyelonephritis (upper UTI), rather than cystitis (lower UTI), is suggested by fever $\geq 38.5^{\circ}\text{C}$ (especially if lasting >48 hours after initiating appropriate antibiotics), systemic symptoms, costovertebral angle tenderness, elevated CRP, leukocytosis.

G. Imaging

1. **Renal and bladder ultrasound (RBUS):** Evaluates for anatomic abnormalities and abscesses. Indications include children 2 to 24 months with first UTI, recurrent or atypical UTIs, or if no response to treatment within 48 hours. If there is clinical improvement <48 hours and follow up is reliable, should be done after full recovery. If there is no response to treatment or follow up is uncertain, then RBUS during illness is indicated.
2. **Voiding cystourethrography (VCUG):** Evaluates bladder anatomy, emptying, and looks for signs of vesicoureteral reflux (VUR). Should not be obtained routinely after first febrile UTI. Indications include children 2 to 24 months with abnormal RBUS findings (hydronephrosis, scarring, or other findings suggestive of either high-grade VUR or obstructive uropathy), complicated or recurrent pyelonephritis.⁸ Consider if family history of VUR. Optimal time is 2 to 6 weeks after infection.

H. Treatment of Culture-Positive Urinary Tract Infection

For empiric therapy, see Chapter 17.

1. Organisms:

- a. *E. coli* is the most common cause of pediatric UTI.
- b. Other common pathogens: *Klebsiella*, *Proteus* spp., *Staphylococcus saprophyticus*, and *Staphylococcus aureus*.
- c. Neonatal UTI: Group B streptococci and other bloodborne pathogens.
- d. *Enterococcus* and *Pseudomonas* are more prevalent in abnormal hosts (e.g., recurrent UTI, abnormal anatomy, neurogenic bladder, hospitalized patients, or those with frequent bladder catheterizations). Consider blood cultures if urine grows uncommon organism or *Staphylococcus*.

2. Treatment considerations and duration:

- a. Route: Parenteral antibiotics for children who are toxic, dehydrated, or unable to tolerate oral medication due to vomiting or noncompliance.

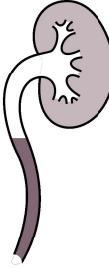
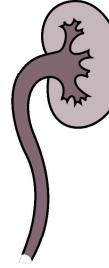
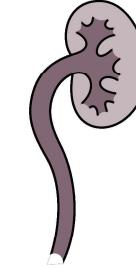
Grade I	Grade II	Grade III	Grade IV	Grade V
				

FIGURE 19.1

International classification of vesicoureteral reflux. (Modified from Rushton H. Urinary tract infections in children: epidemiology, evaluation, and management. *Pediatr Clin North Am.* 1997;44:5 and International Reflux Committee. Medical vs. surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics.* 1981;67:392.)

- b. Duration: 3 to 5 days for uncomplicated cases¹²; 7 to 14 days for toxic children and those with pyelonephritis.
- 3. **Inadequate response to therapy:** Consider renal abscess or urinary obstruction; RBUS and repeat urine culture is indicated. Repeat cultures should also be considered in patients with recurrent UTIs to rule out persistent bacteriuria.
- 4. **Management of VUR:**
 - a. Classification of VUR: Fig. 19.1
 - b. Antibiotic prophylaxis: Evidence suggests that prophylactic trimethoprim-sulfamethoxazole reduces the risk of UTI recurrence by 50%, but with no significant difference in renal scarring. Some experts suggest that recent studies are insufficiently powered to detect a difference in the relatively rare outcomes of renal

- scarring, and thus recommend shifting guideline recommendations from “no prophylaxis” to “selective prophylaxis” in certain groups of patients.¹³
- c. Surgical intervention: Monitor persistence/grade of VUR annually, often in consultation with a pediatric urologist. Spontaneous resolution may occur, although less likely with higher grade. Higher-grade VUR that persists as the child grows may ultimately require surgical intervention.
 - 5. **Asymptomatic bacteriuria:** Defined as bacteria in urine on microscopy and Gram stain in an afebrile, asymptomatic patient without pyuria. Antibiotics not necessary if voiding habits and urinary tract are normal.
 - 6. **Referral to pediatric urology:** Consider in children with abnormal voiding patterns based on history or imaging, neurogenic bladder, abnormal anatomy, recurrent UTI, or poor response to appropriate antibiotics.

V. PROTEINURIA^{14–16}

A. Definitions

1. **Orthostatic proteinuria:** Excretion of significant amounts of protein while in the upright position. A benign condition and common cause of proteinuria in children and adolescents.
2. **Fixed proteinuria:** Proteinuria found on first morning urine void over several consecutive days. Suggestive of kidney disease.
3. **Microalbuminuria:** Presence of albumin in urine below detectable range of dipsticks. In adults, defined as 30 to 300 mg/g creatinine. Most often used in screening for kidney disease secondary to diabetes.
4. **Significant proteinuria:** Urine protein to urine creatinine (UPr:UCr) ratio 0.2 to 2.0 mg/mg or 4 to 40 mg/m²/hr in a 24-hour collection.
5. **Nephrotic-range proteinuria:** UPr:UCr ratio >2 mg/mg or >40 mg/m²/hr in a 24-hour collection. In adults, 24-hour urine protein excretion of 3000 mg/24 hours.
6. **Nephrotic syndrome:** Nephrotic-range proteinuria, hypoalbuminemia, edema, and hyperlipidemia (cholesterol >200 mg/dL).

B. Methods of Detection

1. **Urinalysis** (see Table 19.1): Proteinuria on a urine dipstick should be verified by a urine protein/creatinine ratio in an appropriately collected first morning urine specimen. Urine samples collected immediately upon rising in the morning help distinguish the contribution of benign orthostatic proteinuria to the proteinuria detected on dipstick or randomly timed spot urine collection.
2. **First morning urine protein/creatinine ratio:**
 - a. Approximates 24-hour urine collections well.
 - b. Appropriate collection is essential for accurate results. A child must empty the bladder before going to bed. If the child gets up during the night, the bladder should be emptied before returning to bed. When the child wakes up in the morning, the urine sample should be provided immediately.

BOX 19.1**CAUSES OF PROTEINURIA**

Transient proteinuria: Caused by fever, exercise, dehydration, cold exposure, seizure, stress

Orthostatic proteinuria

Glomerular diseases with isolated proteinuria: Idiopathic (minimal change disease) nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, amyloidosis, diabetic nephropathy, sickle cell nephropathy

Glomerular diseases with proteinuria as a prominent feature: Acute postinfectious glomerulonephritis, immunoglobulin A nephropathy

Tubular disease: Cystinosis, Wilson disease, acute tubular necrosis, tubulointerstitial nephritis, polycystic kidney disease, renal dysplasia, toxic tubular injury (medications, heavy metals)

Adapted from Kliegman RM, Stanton BF, St. Geme JW, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2015.

- c. Normal ratios:
 - (1) <2 years old: <0.5 mg/mg
 - (2) >2 years old: <0.2 mg/mg
- d. Abnormal ratios (mg/mg): Significant proteinuria detected on a first morning protein/creatinine ratio should prompt verification of appropriate collection. Repeat specimen should be analyzed within 1 to 2 weeks, or sooner based on clinical scenario (e.g., edema, hypertension, or symptom of concern would prompt a more expedited workup).
- 3. **24-hour urine protein:** May have a contribution from benign orthostatic proteinuria, which cannot be ruled out without a fractional urine collection. Protein level >4 mg/m²/hr is considered significant.

C. Etiologies (Box 19.1)

See Section VI.E for discussion of nephrotic syndrome.

D. Evaluation¹⁵

Further evaluation is necessary if proteinuria is significant/symptomatic and not secondary to orthostatic proteinuria (Box 19.2).

E. Nephrotic Syndrome¹⁶

1. **Epidemiology:** Idiopathic nephrotic syndrome of childhood is the most common form, representing approximately 90% of cases in children between the ages of 1 and 10 years. *Minimal change disease* is the most common renal pathology found among children with idiopathic nephrotic syndrome in this age group. Nephrotic syndrome may be a manifestation of a primary kidney disease, a systemic disorder resulting in glomerular injury, or rarely medication.
2. **Clinical manifestations:** Hypoalbuminemia and decrease in oncotic pressure results in generalized edema. Initial swelling commonly occurs on the face (especially periorbital), as well as in the pretibial area. Eye swelling is often mistaken for allergic reactions or seasonal allergies (Box 19.3).

BOX 19.2**BASIC EVALUATION OF SIGNIFICANT (NEPHROTIC AND NONNEPHROTIC) PROTEINURIA**

Complete metabolic panel with phosphorus
 C3 and C4
 ESR, CRP
 Antinuclear antibody, anti–double stranded DNA antibody
 Hepatitis B, C, and HIV in high-risk populations
 Antineutrophil antibodies (c- and p-ANCA)
 Lipid panel
 Renal and bladder ultrasonography
 Referral to nephrologist

BOX 19.3**FACTORS SUGGESTING DIAGNOSIS OTHER THAN IDIOPATHIC MINIMAL CHANGE NEPHROTIC SYNDROME**

Age <1 year or >10 years
 Family history of kidney disease
 Extrarenal disease (arthritis, rash, anemia)
 Chronic disease of another organ or systemic disease
 Symptoms due to intravascular volume expansion (hypertension, pulmonary edema)
 Kidney failure
 Active urine sediment (red blood cell casts)

TABLE 19.8**ETIOLOGIES OF NEPHROTIC SYNDROME**

Primary Causes (90%)	Secondary Causes (10%)
Minimal change nephrotic syndrome (MCNS): 85% of idiopathic causes in children	Infections (HIV, hepatitis B, hepatitis C)
Focal segmental glomerulosclerosis (FSGS)	Systemic lupus erythematosus
Membranous nephropathy	Diabetes mellitus
IgA nephropathy	Drugs
Genetic disorders involving the slit diaphragm	Malignancy (leukemias, lymphomas)

3. **Etiologies:** See Table 19.8.
4. **Investigations at first presentation:** UA and microscopy (microhematuria present in 30% and is not prognostic); urine P/Cr ratio; serum albumin, total protein, cholesterol, creatinine; infectious workup (consider tuberculosis, HIV, hepatitis B, hepatitis C, as indicated).
5. **Management of idiopathic nephrotic syndrome of childhood:** Empirical corticosteroid treatment without kidney biopsy is recommended for children without atypical features. Hospitalization recommended for children with overwhelming edema or infection.

- a. Steroid-responsive: Approximately 95% of patients with minimal change disease (MCD) and 20% with focal segmental glomerulosclerosis (FSGS) achieve remission within 4 to 8 weeks of starting prednisone. Response to corticosteroids is the best prognostic indicator, including the likelihood of underlying MCD.
 - (1) Although duration of therapy varies, one common regimen includes prednisone 60 mg/m^2 daily or 2 mg/kg/day (maximum dose 60 mg/day) for 6 weeks, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 6 weeks.¹⁶
 - (2) Relapses of idiopathic nephrotic syndrome are treated with a shorter duration of corticosteroids, which also vary according to the center and the consensus body. Commonly, prednisone 60 mg/m^2 or 2 mg/kg/day (maximum dose 60 mg/day) until urine protein is negative for 3 consecutive days, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 4 weeks.
- b. Frequently relapsing: Defined as 2 or more relapses within 6 months of initial response, or 4 or more relapses in any 12-month period.
- c. Steroid-dependent: Defined as 2 consecutive relapses during tapering or within 14 days of cessation of steroids. Some patients can be managed with low-dose steroids, given daily or on alternate days, but many will relapse. Second-line treatments for frequently relapsing and steroid-dependent nephrotic syndrome: Cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, levamisole, or rituximab.
- d. Steroid-resistant: Lack of remission or partial remission after 8 weeks of corticosteroids. Second-line agents, including calcineurin inhibitors or MMF, are often introduced once steroid resistance is confirmed.
- e. Indications for renal biopsy: Macroscopic hematuria, age <12 months or >12 years, systemic or syndromic findings, persistent creatinine elevation >1 to 2 weeks, low complement levels, and persistent proteinuria after 4 to 8 weeks of adequate steroid treatment.¹⁷

6. Complications:

- a. AKI; thromboembolic disease; potentially life-threatening infection. See Chapter 16 for vaccine recommendations.
- b. Chronic systemic steroids: Cushingoid skin changes, cataracts, accelerated atherosclerosis, osteoporosis, gastric ulcer, mood swings, insomnia, insulin resistance, immunosuppression.

VI. HEMATURIA¹⁸

A. Definition

1. **Microscopic hematuria:** $>5 \text{ RBCs/hpf}$ on centrifuged urine. Not visible to the naked eye.
2. **Macroscopic (gross) hematuria:** Visible blood in urine.
3. **Acute nephritic syndrome:** Classically tea or cola-colored urine, facial or body edema, hypertension, and oliguria.

B. Etiologies: See Table 19.9.

TABLE 19.9**CAUSES OF HEMATURIA IN CHILDREN**

Kidney-related disease	Isolated glomerular disease	IgA nephropathy, Alport syndrome, thin glomerular basement membrane nephropathy, postinfectious/poststreptococcal glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, antiglomerular basement membrane disease
	Multisystem disease involving glomerulus	Systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, granulomatosis with polyangiitis, polyarteritis nodosa, Goodpasture syndrome, hemolytic-uremic syndrome, sickle cell glomerulopathy, HIV nephropathy
	Tubulointerstitial disease	Pyelonephritis, interstitial nephritis, papillary necrosis, acute tubular necrosis
Vascular		Arterial or venous thrombosis, malformations (aneurysms, hemangiomas), nutcracker syndrome, hemoglobinopathy (sickle cell trait/disease)
Anatomical		Hydronephrosis, cystic kidney disease, polycystic kidney disease, multicystic dysplasia, tumor, trauma
Urinary tract disease		Inflammation (cystitis, urethritis) Urolithiasis Trauma Coagulopathy Arteriovenous malformations (AVMs) Bladder tumor Factitious

C. Evaluation (Fig. 19.2)

Differentiate glomerular and extraglomerular hematuria: Examine urine sediment, looking for RBC casts and protein.

1. Glomerular hematuria
 - a. Usually hypertensive; dysuria usually absent; edema, fever, pharyngitis, rash, and arthralgia may suggest glomerular disease.
 - b. Laboratory: Dysmorphic RBCs and casts on UA, complete blood cell count (CBC) with differential and smear, serum electrolytes with calcium, BUN/creatinine, serum protein/albumin, and other testing driven by history and exam, including ANA, hepatitis B and C serologies, HIV, audiology screen, if indicated.
 - c. Consider other studies to determine underlying diagnosis: C3/C4, antineutrophil antibody (c- and p-antineutrophil cytoplasmic antibodies), anti-double-stranded DNA
2. Extraglomerular hematuria
 - a. Rule out infection: Urine culture, gonorrhea, chlamydia
 - b. Rule out trauma: History, consider imaging of abdomen/pelvis
 - c. Investigate other potential causes: Urine Ca/Cr ratio or 24-hour urine for kidney stone risk analysis, sickle cell screen, renal/bladder ultrasound. Consider serum electrolytes with calcium, coagulation studies.

D. Management (Fig. 19.3)

VII. ACUTE KIDNEY INJURY^{19,20}

A. Definition

Sudden decline in kidney function; clinically represented by rising creatinine, with or without changes in urine output.

B. Etiology (Table 19.10)

Causes are generally subdivided into three categories:

1. **Prerenal:** Impaired perfusion of kidneys, the most common cause of acute kidney injury (AKI) in children. Volume depletion is a common cause of prerenal AKI.
2. **Renal:**
 - a. Parenchymal disease due to vascular or glomerular lesions.
 - b. Acute tubular necrosis: Diagnosis of exclusion when no evidence of renal parenchymal disease is present and prerenal and postrenal causes have been eliminated, if possible.
3. **Postrenal:** Obstruction of the urinary tract, commonly due to inherited anatomic abnormalities in children.

C. Clinical Presentation

Pallor, decreased urine output, systemic and pulmonary edema, hypertension, vomiting, and lethargy. The hallmark of early kidney failure is often oliguria.

1. **Oliguria:** Urine output <0.5 mL/kg/hr (for at least 6 hours). May reflect intrinsic or obstructive kidney disease. Always interpret urine output in the context of physical exam, clinical scenario, and fluid delivery.

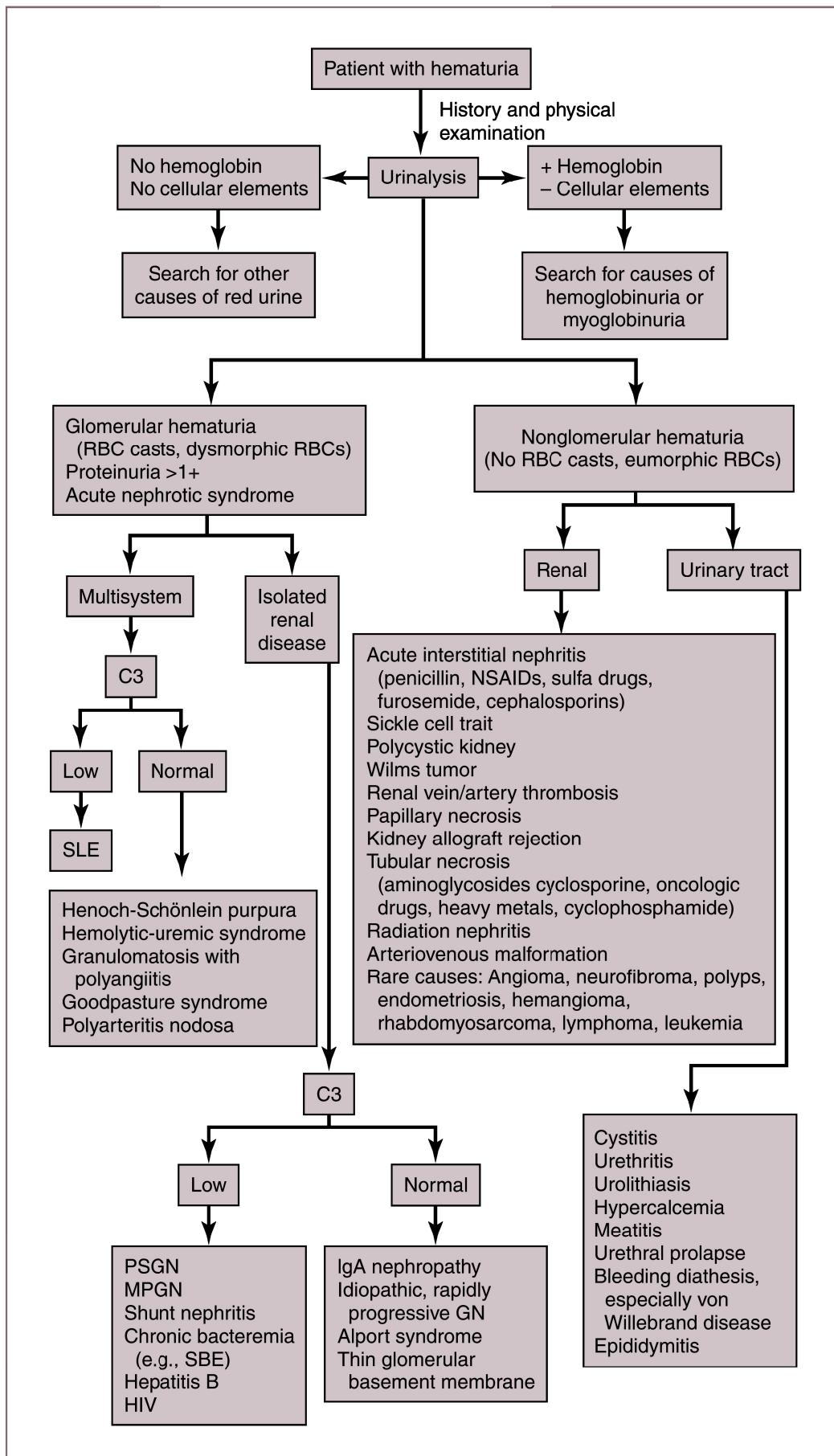
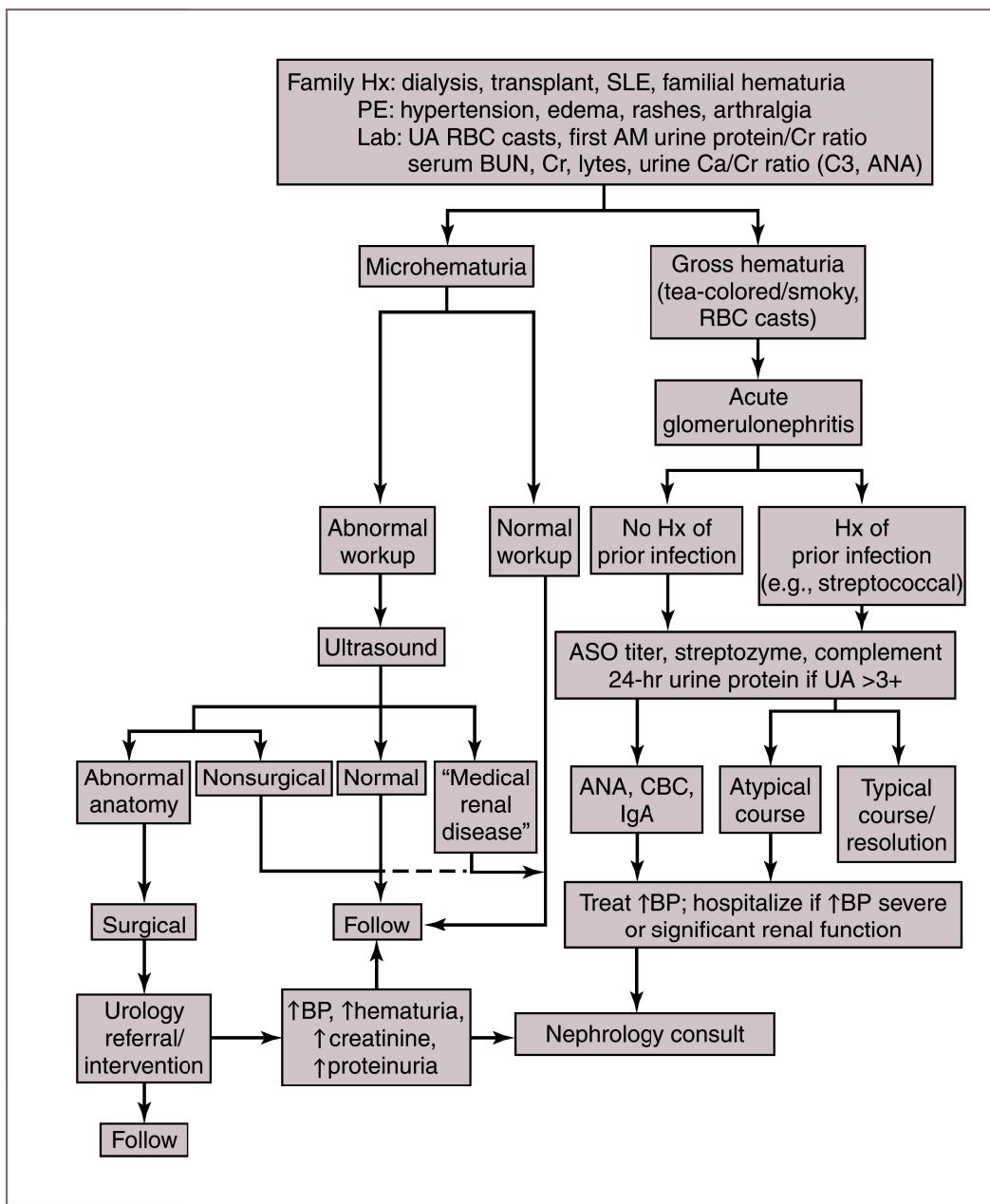


FIGURE 19.2

Diagnostic strategy for hematuria. *GN*, Glomerulonephritis; *HIV*, human immunodeficiency virus; *MPGN*, membranoproliferative glomerulonephritis; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PSGN*, poststreptococcal glomerulonephritis; *RBC*, red blood cell; *SBE*, subacute bacterial endocarditis; *SLE*, systemic lupus erythematosus.

**FIGURE 19.3**

Management algorithm for hematuria. (Data from Hay WM, Levin MJ, Deterding RR, Azbug MJ, Sondheimer JM. *CURRENT Diagnosis & Treatment Pediatrics*. 21st ed. www.accessmedicine.com, Fig. 24.1.)

For example, low urine output may be appropriate (physiologic response to water depletion in a prerenal state) and “normal” urine output may be inappropriate in a volume-depleted patient (potentially representing kidney tubular damage or another pathologic state).

Laboratory differentiation of oliguria is found in [Table 19.11](#).

2. **Blood urea nitrogen/creatinine (BUN/Cr) ratio (both in mg/dL):** Interpret ratios with caution in small children with low serum creatinine.
 - a. 10 to 20 (normal ratio): Suggests intrinsic renal disease in the setting of oliguria.

TABLE 19.10**ETIOLOGIES OF ACUTE KIDNEY INJURY**

PRERENAL	Decreased True Intravascular Volume: Hemorrhage, volume depletion, sepsis, burns Decreased Effective Intravascular Volume: Congestive heart failure, hepatorenal syndrome Altered Golmerular Hemodynamics: NSAIDs, ACE inhibitors (when renal perfusion is already low)
INTRINSIC RENAL	Acute Tubular Necrosis: Hypoxic/ischemic insults Drug-induced—aminoglycosides, amphotericin B, acyclovir, chemotherapeutic agents (ifosfamide, cisplatin) Toxin-mediated—endogenous toxins (myoglobin, hemoglobin); exogenous toxins (ethylene glycol, methanol) Interstitial Nephritis: Drug-induced— β -lactams, NSAIDs (may be associated with high-grade proteinuria), sulfonamides, PPIs Idiopathic Uric acid nephropathy: Tumor lysis syndrome Glomerulonephritis: In most severe degree, presents as rapidly progressive glomerulonephritis (RPGN) Vascular Lesions: Renal artery thrombosis, renal vein thrombosis, cortical necrosis, hemolytic uremic syndrome Hypoplasia/Dysplasia: Idiopathic or exposure to nephrotoxic drugs in utero
POSTRENAL	Obstruction in a Solitary Kidney Bilateral Ureteral Obstruction Urethral Obstruction Bladder Dysfunction

ACE, Angiotensin-converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs; PPIs, proton pump inhibitors.

Data from Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol*. 2009;24:253–263.

TABLE 19.11**LABORATORY DIFFERENTIATION OF OLIGURIA**

Test	Prerenal	Renal
FENa	$\leq 1\%$	$> 3\%$
BUN/Cr ratio	$> 20:1$	$< 10:1$
Urine specific gravity	> 1.015	< 1.010

BUN, Blood urea nitrogen; Cr, creatinine; FENa, fractional excretion of sodium.

- b. > 20 : Suggests volume depletion, prerenal azotemia, or gastrointestinal bleeding.
- c. < 5 : Suggests liver disease, starvation, or inborn error of metabolism.

D. Acute Tubular Necrosis

Clinically defined by three phases:

1. **Oliguric phase:** Period of severe oliguria that may last days. If oliguria or anuria persists for longer than 3 to 6 weeks, kidney recovery from ATN is less likely.
2. **High urine output phase:** Begins with increased urine output and progresses to passage of large volumes of isosthenuric urine containing sodium levels of 80 to 150 mEq/L.
3. **Recovery phase:** Signs and symptoms usually resolve rapidly, but polyuria may persist for days to weeks.

E. Treatment Considerations

1. Careful monitoring of volume status (daily weights, strict input/output). Consider placement of indwelling catheter to monitor urine output.
2. Prerenal and postrenal factors should be addressed or excluded.
3. Intravascular volume resuscitation and maintenance with appropriate fluids in consultation with a pediatric nephrologist.
4. Monitor metabolic/electrolyte abnormalities, discontinue unnecessary nephrotoxic medications and follow drug levels closely when available, adjust dosing of medications based on creatinine clearance (see Chapter 31), monitor blood pressure closely, and maintain appropriate nutrition (low phosphorus, low potassium).
5. See Section IX for indications for acute dialysis

F. Complications

1. Dependent on clinical severity.
2. Usually includes fluid overload (hypertension, congestive heart failure [CHF], or pulmonary edema), electrolyte disturbances (hyperkalemia), metabolic acidosis, hyperphosphatemia, and uremia.

G. Radiographic Imaging Considerations in AKI/CKD

1. To prevent radiographic contrast-induced nephropathy, select radiographic studies that do not require administration of a radiographic iodinated contrast media (RICM) if possible, particularly in high-risk populations, such as patients with AKI or CKD.²¹
2. If RICM is required, use of low or iso-osmolality contrast media is preferred.²¹
3. Hydration has been found to be effective in preventing or minimizing contrast-induced nephropathy in some studies of high-risk populations. Intravenous hydration 6 hours prior to and 6 to 12 hours after contrast administration has been studied.²¹
4. Use of N-acetylcysteine is controversial in preventing contrast-induced nephropathy.²¹
5. Gadolinium and nephrogenic systemic fibrosis: The triad of gadolinium use, a pro-inflammatory state, and renal impairment (GFR <30 mL/min per 1.73 m², peritoneal or hemodialysis) is associated with nephrogenic

systemic fibrosis. Gadolinium is contraindicated in patients with GFR <30 mL/min per 1.73 m², and caution should be used at GFR levels between 30 and 60 mL/min per 1.73 m².²²

VIII. CHRONIC KIDNEY DISEASE²³

A. Definition

Kidney damage for >3 months, as defined by structural or functional abnormalities, with or without decreased GFR. Classified as:

- Stage I: Kidney injury with normal or increased GFR
- Stage II: GFR 60 to 89 mL/min/1.73 m²
- Stage III: GFR 30 to 59 mL/min/1.73 m²
- Stage IV: GFR 15 to 29 mL/min/1.73 m²
- Stage V: GFR <15 mL/min/1.73 m² or dialysis

B. Etiology

1. Children <5 years: Most commonly due to congenital abnormalities (e.g., kidney hypoplasia/dysplasia, urologic malformations).
2. Older children: More commonly acquired glomerular diseases (e.g., glomerulonephritis, FSGS) or hereditary disorders (e.g., Alport syndrome).

C. Clinical Manifestations (Table 19.12)

D. General Management

1. **Nutrition:** Growth should be monitored closely; supplemental nutrition should be considered if not reaching caloric goals, which are higher in children with CKD. Potassium and sodium restriction may be required in advanced CKD. Growth hormone therapy may be considered in consultation with pediatric nephrology/endocrinology.
2. **Anemia:** Evaluate with CBC and iron studies. Iron deficiency is common and should be treated with oral (preferred) or IV iron. Consider erythropoietin-stimulating agents in consultation with pediatric nephrology.
3. **CKD–mineral and bone disorder:** Characterized by phosphate retention, decreased free calcium, and decreased 1,25 hydroxyvitamin D. Serum calcium, phosphate, alkaline phosphatase, vitamin D, and parathyroid hormone should be regularly monitored. Control phosphate with phosphate binders, supplement with calcium and vitamin D, as indicated.
4. **Cardiovascular:** Regularly monitor blood pressure and lipid panel. Treating hypertension slows the progression of CKD.

IX. DIALYSIS

A. Indications for Acute Dialysis

When metabolic or fluid derangements are not controlled by aggressive medical management alone. Should be initiated in consultation with a nephrologist. Generally accepted criteria include the following:

1. **Acidosis:** Intractable metabolic acidosis.

TABLE 19.12
CLINICAL MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

Manifestation	Mechanisms
Edema	Accumulation of Na^+ and water Decreased oncotic pressure Reduced cardiac output Mineralocorticoid excess
Uremia	Decline in GFR
Acidosis	Urinary bicarbonate wasting Decreased excretion of NH_4 and acid
Sodium wasting	Solute diuresis, tubular damage Aldosterone resistance
Sodium retention	Nephrotic syndrome CHF Reduced GFR
Urinary concentrating defect	Solute diuresis, tubular damage ADH resistance
Hyperkalemia	Decline in GFR, acidosis Aldosterone resistance
Renal osteodystrophy	Impaired production of 1,25(OH) vitamin D Decreased intestinal calcium absorption Impaired phosphorus excretion Secondary hyperparathyroidism
Growth retardation	Protein-calorie deficiency Renal osteodystrophy Acidosis Anemia Inhibitors of insulin-like growth factors
Anemia	Decreased erythropoietin production Low-grade hemolysis Bleeding, iron deficiency Decreased erythrocyte survival Inadequate folic acid intake Inhibitors of erythropoiesis
Bleeding tendency	Thrombocytopenia Defective platelet function
Infection	Defective granulocyte function Glomerular loss of immunoglobulin/opsonins
Neurologic complaints	Uremic factors
Gastrointestinal ulceration	Gastric acid hypersecretion/gastritis Reflux Decreased motility
Hypertension	Sodium and water overload Excessive renin production
Hypertriglyceridemia	Diminished plasma lipoprotein lipase activity
Pericarditis and cardiomyopathy	Unknown
Glucose intolerance	Tissue insulin resistance

ADH, Antidiuretic hormone; CHF, congestive heart failure; GFR, glomerular filtration rate; NH_4 , ammonium.

Adapted from Brenner BM. *Brenner and Rector's The Kidney*. 10th ed. Philadelphia: Elsevier; 2015.

2. **Electrolyte abnormalities:** Hyperkalemia >6.5 mEq/L despite restriction of delivery and medical management; calcium and phosphorus imbalance (e.g., hypocalcemia with tetany, seizures in the presence of a very high serum phosphate level); derangements implicated in neurologic abnormalities.
3. **Ingestion or accumulation of dialyzable toxins or poisons:** Lithium, ammonia, alcohol, barbiturates, ethylene glycol, isopropanol, methanol, salicylates, theophylline. Consult poison control experts when available.
4. **Volume overload:** Evidence of pulmonary edema or hypertension.
5. **Uremia:** BUN >150 mg/dL (lower if rising rapidly), uremic pericardial effusion, neurologic symptoms.

B. Techniques

1. **Peritoneal dialysis (PD):** Requires catheter to access peritoneal cavity, as well as adequate peritoneal perfusion. May be used acutely or chronically. Contraindications: Abdominal wall defects (omphalocele, gastroschisis, bladder exstrophy, diaphragmatic hernia), severe inflammatory bowel disease, or infectious source in the abdomen.²⁴
2. **Intermittent hemodialysis (HD):** Requires placement of special vascular access catheters. May be method of choice for certain toxins (e.g., ammonia, uric acid, poisons) or when there are contraindications to peritoneal dialysis.
3. **Continuous arteriovenous hemofiltration/hemodialysis (CAVH/D) and continuous venovenous hemofiltration/hemodialysis (CVVH/D):** Requires special vascular access catheter. Lower efficiency of solute removal compared with intermittent hemodialysis, but higher efficiency is not necessary because of the continuous nature of this form of dialysis. Sustained nature of dialysis allows for more gradual removal of volume/solutes, which is ideal for patients with hemodynamic or respiratory instability.

C. Complications

1. **PD catheter leaks:** Confirm leakage of PD fluid with glucose dipstick. Discontinue PD for 7 to 10 days or lower dialysate volume.
2. **PD associated peritonitis (PDAP):** Acute clouding of dialysate, abdominal pain/distention, vomiting. Culture peritoneal fluid and start empiric intra-peritoneal antibiotics in consultation with nephrology. Refer to published Consensus Guidelines for treatment recommendations.²⁵
3. **Intradialytic hypotension in HD:** Causes include rapid fluid removal, pre-dialysis antihypertensive medication, bradykinin release, hypotonic dialysate. Reduce or pause ultrafiltration.

X. TUBULAR DISORDERS

A. Renal Tubular Acidosis (Table 19.13)²⁶

1. A group of transport defects resulting in abnormal urine acidification; due to defects in reabsorption of bicarbonate (HCO_3^-), excretion of hydrogen ions (H^+), or both.

TABLE 19.13
RENAL TUBULAR ACIDOSIS BIOCHEMICAL AND CLINICAL CHARACTERISTICS

	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Hypoaldosteronism)
Mechanism	Impaired distal acidification	Impaired bicarbonate absorption	Decreased aldosterone secretion or aldosterone effect
Etiology	Hereditary Sickle cell disease Toxins/drugs Cirrhosis Obstructive uropathy Connective tissue disorder	Hereditary Metabolic disease Fanconi syndrome Prematurity Toxins/heavy metals Amyloidosis PNH	Absolute mineralocorticoid deficiency Adrenal failure CAH DM Pseudohypoaldosteronism Interstitial nephritis
Minimal urine pH	>5.5	<5.5 (urine pH can be >5.5 with a bicarbonate load)	<5.5
Fractional excretion of bicarbonate (FeHCO_3)	↓ (<5%)	↑ (>15%)	↓ (<5%)
Plasma K ⁺ concentration	Normal or ↓	Usually ↓	↑
Urine anion gap	Positive	Positive or negative	Positive
Nephrocalcinosis/nephrolithiasis	Common	Rare	Rare
Treatment	1–3 mEq/kg/day of HCO_3 (5–10 mEq/kg/day if bicarb wasting)	5–20 mEq/kg/day of HCO_3	1–5 mEq/kg/day of HCO_3 May add fludrocortisone and potassium binders

CAH, Congenital adrenal hyperplasia; DM, diabetes mellitus; PNH, paroxysmal nocturnal hemoglobinuria.

Adapted from Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein LS. *Pediatric Nephrology*. Baltimore: Springer-Verlag Berlin Heidelberg; 2016.

2. Results in a persistent normal anion gap hyperchloremic metabolic acidosis.
3. RTA syndromes have a normal GFR and often do not progress to kidney failure.
4. Clinical presentation may be characterized by failure to thrive, polyuria, constipation, vomiting, and dehydration.
5. **Fractional excretion of bicarbonate (FeHCO_3) should be checked after a HCO_3 load.** Can help differentiate the types of RTA. See Section II.B for equation.
6. **Urine anion gap (UAG) is also useful;** however, it should not be used when a patient is volume depleted or has an anion-gap metabolic acidosis. See Section II.B for equation.

B. Fanconi Syndrome

- Generalized dysfunction of the proximal tubule resulting not only in bicarbonate loss but also in variable wasting of phosphate, glucose, and amino acids.
- May be hereditary, as in cystinosis and galactosemia, or acquired through toxin injury and other immunologic factors.
- Clinically characterized by rickets and impaired growth.

C. Nephrogenic Diabetes Insipidus

- Water conservation is dependent on antidiuretic hormone (ADH) and its effects on the distal renal tubules.** Polyuria (urine output >5 mL/kg/hr or >2 L/day), a hallmark of nephrogenic diabetes insipidus (NDI), is due to diminished or lack of response of the ADH receptor in the distal renal tubules. Hereditary defects of ADH receptor or acquired insults (e.g., interstitial nephritis, sickle cell disease, lithium toxicity, CKD) may underlie NDI.
- Must be differentiated from other causes of polyuria:** Central diabetes insipidus (ADH deficiency that may be idiopathic or acquired through infection or pituitary trauma; see Chapter 10), diabetes mellitus, psychogenic polydipsia, cerebral salt wasting.

XI. NEPHROLITHIASIS²⁷⁻³⁰

A. Risk Factors

Male sex; history of UTI (especially those <5 years); congenital and structural urologic abnormalities (urinary stasis), neurogenic bladder, hypercalciuria, hyperoxaluria/oxalosis, hypocitraturia, other metabolic abnormalities; family history of stones, renal failure, consanguinity.

B. Presentation

- Microscopic hematuria (90%), flank/abdominal pain (50% to 75%), gross hematuria (30% to 55%), and concomitant UTI in up to 20%.
- Have higher likelihood than adults of having asymptomatic stones, especially younger children.

C. Diagnostic Imaging

- Ultrasonography is an effective and preferred modality, particularly at centers with expertise, given benefit of avoiding radiation exposure (75% sensitive for renal stones).²⁹
- Noncontrast CT may be preferred to improve diagnostic sensitivity (e.g., with radiolucent stones such as uric acid stones, ureteral stones, lack of ultrasonographic expertise).

D. Management

- Pain control, urine culture, hydration.** Some centers initiate α -blockers to facilitate stone passage, although evidence of benefit in children is equivocal.³⁰⁻³²

2. **Antibiotics:** Should be considered in treatment of all stones, especially if fever and/or pyuria present, because of the high association with UTI.
3. **Urologic intervention** (e.g., extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy): Consider with unremitting pain, urinary obstruction, increasing stone size, size ≥ 7 mm, or cystine/struvite stone, especially in the setting of AKI or at-risk patients (e.g., solitary kidney, anatomic anomalies).³²
4. **Strain urine to collect stone; analyze stone composition to aid in prevention of future stones.**

E. Workup

1. Up to 75% of children with a kidney stone will have a metabolic abnormality (e.g., hypercalciuria, hyperoxaluria, hyperuricosuria, cystinuria).
2. Workup should include analysis of the stone (if possible); UA; basic metabolic panel; and serum calcium, phosphate, magnesium, and uric acid levels. If evidence of elevated calcium or phosphate, obtain parathyroid hormone (PTH) level and consider checking 25- and 1,25(OH) vitamin D levels.
3. After symptoms have resolved, a 24-hour urine collection should be obtained. Risk factors for stone formation should be analyzed: urine volume, osmolarity, sodium, calcium, urate, oxalate, citrate, and cystine. This test is also referred to as a “stone risk analysis.”

F. Prevention

1. **All children with history of stones should increase fluid intake** (e.g., at least 2 L/day in those aged >10 years old).
2. **Targeted interventions of any identified metabolic abnormalities** (e.g., low-sodium diet in those with hypercalciuria). Pharmacologic interventions are also available in certain scenarios (e.g., citrate supplementation).
3. **Dietary Modifications:** Long-term adherence (5 years) to normal calcium, low-sodium diet may decrease recurrence of stones in people with idiopathic hypercalciuria with recurrent nephrolithiasis.³³

XII. WEB RESOURCES

- A. International Pediatric Nephrology Association: www.ipna-online.org
- B. National Kidney Disease Education Program: <https://www.niddk.nih.gov/health-information/communication-programs/nkdep>
- C. National Kidney Foundation: www.kidney.org

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A complete list of references can be found online at www.expertconsult.com.

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