49 - 55 Azotemia and Urinary Abnormalities

55 Azotemia and Urinary Abnormalities

diagnosis of exclusion is based largely on history and physical examina tion and its treatment is based on a minimally invasive algorithm, with the focus on the patient’s clinical phenotype and the initial implemen tation of conservative therapeutic measures, IC/BPS can be well man aged even in resource-poor settings. As with many poorly understood and difficult-to-treat conditions, the greatest barrier to its diagnosis and treatment may perhaps be its recognition. ■ ■FURTHER READING Clemens JQ et al: Urologic chronic pelvic pain syndrome: Insights from the MAPP Research Network. Nat Rev Urol 16:187, 2019. Clemens JQ et al: AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 208:34, 2022. Cox A et al: CUA guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Can Urol Assoc J 10:E136, 2016. Moldwin RM et al: Interstitial cystitis/bladder pain syndrome and related disorders, in Campbell-Walsh-Wein Urology, 12th ed. AW Partin et al (eds). Philadelphia, Elsevier, 2021. Nickel JC et al: MV140 sublingual vaccine reduces recurrent urinary tract infection in women. Results from the first North American clinical experience study. Can Urol Assoc J 18:25, 2024. David B. Mount

Azotemia and Urinary Abnormalities Normal kidney functions occur through numerous cellular processes to maintain body homeostasis. Disturbances in any of these functions can lead to abnormalities that may be detrimental to survival. Clini cal manifestations of these disorders depend on the pathophysiology of renal injury and often are identified as a complex of symptoms, abnormal physical findings, and laboratory changes that constitute specific syndromes. These renal syndromes (Table 55-1) may arise from systemic illness or as primary renal disease. Nephrologic syn dromes usually consist of several elements that reflect the underlying pathologic processes, typically including one or more of the following: (1) reduction in glomerular filtration rate (GFR), (2) abnormalities of urine sediment (red blood cells [RBCs], white blood cells [WBCs], casts, and crystals), (3) abnormal urinary excretion of serum proteins (proteinuria), (4) disturbances in urine volume (oliguria, anuria, poly uria), (5) presence of hypertension and/or expanded total body fluid volume (edema), (6) electrolyte abnormalities, and (7) in some syn dromes, fever/pain. The specific combination of these findings should permit identification of one of the major nephrologic syndromes (Table 55-1) and allow differential diagnoses to be narrowed so that the appropriate diagnostic and therapeutic course can be determined. All these syndromes and their associated diseases are discussed in more detail in subsequent chapters. This chapter focuses on several aspects of renal abnormalities that are critically important for distinguishing among those processes: (1) reduction in GFR, (2) alterations of the urinary sediment and/or protein excretion, and (3) abnormalities of urinary volume. AZOTEMIA ■ ■ASSESSMENT OF GFR Monitoring the GFR

is important in both hospital and outpatient set tings, and several different methodologies are available. GFR is the pri mary metric for kidney “function,” and its direct measurement involves administration of a radioactive isotope (such as inulin or iothalamate)

that is filtered at the glomerulus into the urinary space but is neither reabsorbed nor secreted throughout the tubule. GFR—i.e., the clear ance of inulin or iothalamate in milliliters per minute—is calculated from the rate of appearance of the isotope in the urine over several hours. In most clinical circumstances, direct GFR measurement is not feasible, and the plasma creatinine level is used as a surrogate to esti mate GFR. Plasma creatinine (PCr) is the most widely used marker for GFR, which is related directly to urine creatinine (UCr) excretion and inversely to PCr. On the basis of this relationship (with some important caveats, as discussed below), GFR will fall in roughly inverse propor tion to the rise in PCr. Failure to account for GFR reductions in drug dosing can lead to significant morbidity and death from drug toxicities (e.g., digoxin, imipenem). In the outpatient setting, PCr serves as an estimate for GFR (although much less accurate; see below). In patients with chronic progressive renal disease, there is an approximately linear relationship between 1/PCr (y axis) and time (x axis). The slope of that line will remain constant for an individual; when values deviate, an investigation for a superimposed acute process (e.g., volume depletion, drug reaction) should be initiated. Signs and symptoms of uremia, the clinical symptom complex associated with renal failure, develop at significantly different levels of PCr, depending on the patient (size, age, and sex), underlying renal disease, existence of concurrent diseases, and true GFR. Generally, patients do not develop symptomatic uremia until renal insufficiency is severe (GFR <15 mL/min).

Azotemia and Urinary Abnormalities CHAPTER 55 A significantly reduced GFR (either acute or chronic) is usually reflected in a rise in PCr, leading to retention of nitrogenous waste products (defined as azotemia) such as urea. Azotemia may result from reduced renal perfusion, intrinsic renal disease, or postrenal processes (ureteral obstruction; see below and Fig. 55-1). Precise determination of GFR is problematic, as both commonly measured indices (urea and creatinine) have characteristics that affect their accuracy as markers of clearance. Urea clearance may underestimate GFR significantly because of urea reabsorption by the tubule. In contrast, creatinine is derived from muscle metabolism of creatine, and its generation varies little from day to day. Creatinine clearance (CrCl), an approximation of GFR, is measured from plasma and urinary creatinine excretion rates for a defined period (usually 24 h) and is expressed in milliliters per minute: CrCl = (Uvol × UCr)/(PCr × Tmin). The “adequacy” or “completeness” of the urinary collection is estimated by the urinary volume and creatinine content; creatinine is produced from muscle and excreted at a relatively con stant rate. For a 20- to 50-year-old man, creatinine excretion should be 18.5–25.0 mg/kg body weight; for a woman of the same age, it should be 16.5–22.4 mg/kg body weight. For example, an 80-kg man should excrete between ~1500 and 2000 mg of creatinine in an “adequate” col lection. Creatinine is useful for estimating GFR because it is a small, freely filtered solute that is not reabsorbed by the tubules. PCr levels can increase acutely from dietary ingestion of cooked meat, however, and creatinine can be secreted into the proximal tubule through an organic cation pathway (especially in advanced progressive chronic kidney disease [CKD]), leading to overestimation of GFR. When a timed col lection for CrCl is not available, decisions about drug dosing must be based on PCr alone. Two formulas are used widely to estimate kidney function from PCr: (1) Cockcroft-Gault and (2) four-variable MDRD (Modification of Diet in Renal Disease). Cockcroft-Gault: CrCl(mL/min) (140 age) Lean Body Weight (kg) Serum Creatinine (mg/dL)

(0.85 if female)

− × × × MDRD: eGFR (mL/min per 1.73 m2) = 186.3 × PCr (e−1.154) × age (e−0.203) × (0.742 if female) × (1.21 if black). Numerous websites are available to assist with these calcula tions (www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). A newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) esti mated GFR (eGFR), which was developed by pooling several cohorts

TABLE 55-1 Initial Clinical and Laboratory Database for Defining Major Syndromes in Nephrology SYNDROME IMPORTANT CLUES TO DIAGNOSIS COMMON FINDINGS Acute or rapidly progressive renal failure Anuria Hypertension, hematuria 321, 326, 328, 331 Oliguria Proteinuria, pyuria Documented recent decline in GFR Casts, edema Acute nephritis Hematuria, RBC casts Proteinuria

Azotemia, reduced GFR, oliguria Pyuria Edema, hypertension Circulatory congestion PART 2 Cardinal Manifestations and Presentation of Diseases Chronic renal failure Azotemia for >3 months Proteinuria, casts

Symptoms or signs of uremia, (late manifestation), casts Symptoms or signs of renal osteodystrophy Polyuria, nocturia Kidneys reduced in size bilaterally Edema, hypertension Broad casts in urinary sediment Hyperkalemia, metabolic acidosis Nephrotic syndrome Proteinuria, with >3.5 g/24 h per 1.73 m2 Casts

Hypoalbuminemia Lipiduria Edema Hypercoagulable state Hyperlipidemia Asymptomatic urinary abnormalities Hematuria

Proteinuria (below nephrotic range) Sterile pyuria, casts Urinary tract infection/pyelonephritis Bacteriuria, with >105 cfu/mL Hematuria

Other infectious agent documented in urine Mild azotemia and reduced GFR Pyuria, leukocyte casts Mild proteinuria Frequency, urgency Fever Bladder tenderness, flank tenderness Renal tubular defects Electrolyte disorders Hematuria 327, 328 Polyuria, nocturia “Tubular” proteinuria (<1 g/24 h) Renal calcification Enuresis Large kidneys Electrolyte and/or acid-base abnormalities Renal transport defects Other electrolyte issues, e.g., hypomagnesemia Hypertension Systolic/diastolic hypertension Proteinuria 288, 329 Casts Azotemia Nephrolithiasis Previous history of stone passage or removal Hematuria

Previous history of stone seen by x-ray Pyuria Renal colic Frequency, urgency Urinary tract obstruction Azotemia, oliguria, anuria Hematuria

Polyuria, nocturia, urinary retention Pyuria Slowing of urinary stream Enuresis, dysuria Large prostate, large kidneys Flank tenderness, full bladder after voiding Abbreviations: cfu, colony-forming units; GFR; glomerular filtration rate; RBC, red blood cell. with and without kidney disease who had data on directly measured GFR, appears to be more accurate: CKD-EPI: eGFR = 141 × min (PCr/k, 1)a × max (PCr/k, 1)−1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black], where PCr is

plasma creatinine, k is 0.7 for females and 0.9 for males, a is –0.329 for females and –0.411 for males, min indicates the minimum of PCr/k or 1, and max indicates the maximum of PCr/k or 1 (https://www. mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr). There are limitations to all creatinine-based estimates of GFR. Each equation, along with 24-h urine collection for measurement of creati nine clearance, is based on the assumption that the patient is in steady state, without daily increases or decreases in PCr as a result of rapidly changing GFR. The MDRD equation is better correlated with true GFR when the GFR is <60 mL/min per 1.73 m2. The gradual loss of muscle

CHAP(S). DISCUSSING DISEASE-CAUSING SYNDROME Hypocalcemia, hyperphosphatemia, hyperparathyroidism from chronic illness, chronic use of glucocorticoids, or malnutrition can mask significant changes in GFR with small or imperceptible changes in PCr. The coefficient of 1.159 in the CKD-EPI equation to adjust for self-reported black race reflects that measured GFR was 16% higher in blacks than nonblacks with similar age, sex, and creatinine in the data set used to develop the equation. Race is a social rather than a biological construct, for which reason the use of the “race modifier” in calculating eGFR using CKD-EPI and other equations has come under scrutiny. In particular, given the implications of utilizing selfreported race to modify clinical laboratory results, many medical centers have recently stopped reporting eGFRs that have been calcu lated using a race modifier. This change is projected to have positive consequences, in particular, improved access to waitlisting for renal transplantation in black patients at an earlier stage of CKD. Potential

AZOTEMIA Urinalysis and renal ultrasound Hydronephrosis Renal size parenchyma Urinalysis Urologic evaluation Relieve obstruction Normal size kidneys Intact parenchyma Bacteria Pyelonephritis Small kidneys, thin cortex, bland sediment, isosthenuria <3.5 g protein/24 h Acute Renal Failure Normal urinalysis with oliguria Chronic Renal Failure Symptomatic treatment delay progression If end-stage, prepare for dialysis Urine electrolytes Muddy brown casts, amorphous sediment

- protein FeNa <1% U osmolality >500 mosmol FeNa >1% U osmolality <350 mosmol Renal biopsy Prerenal Azotemia Volume contraction, cardiac failure, vasodilatation, drugs, sepsis, renal vasoconstriction, impaired autoregulation Acute Tubular Necrosis Glomerulonephritis or vasculitis Immune complex, anti-GBM disease FIGURE 55-1 Approach to the patient with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane; RBC, red blood cell; U, urine; WBC, white blood cell. negative consequences include “overdiagnosis” of CKD, inadequate or inaccurate dosing of drugs that are eliminated through the kidney (e.g., metformin), reduced access to imaging modalities for black patients with CKD with a lower reported eGFR, and reductions in living kidney donation among blacks. These and the other limitations in creatinine-based eGFR have led to the development of alternative methods for estimat ing GFR. Cystatin C, a member of the cystatin superfamily of cysteine prote ase inhibitors, is produced at a relatively constant rate from all nucle ated cells. Serum cystatin C has been proposed to be a more sensitive marker of early GFR decline than is PCr, with lesser effects of muscle mass on circulating levels; however, cystatin C levels are influenced by the patient’s sex and the presence of diabetes mellitus, smoking, and inflammation. To the extent that cystatin C–based calculation of eGFR is less affected by self-reported race

and muscle mass, it is an increas ingly important adjunct to creatinine-based eGFR. Recently, eGFR equations that include both creatinine and cystatin C have been shown to be more accurate than the single-measurement equations. Clinical judgement and clinical assessment also play an important role in inter preting eGFR values. For example, a bodybuilder may have an elevated creatinine level due to increased muscle mass, with an underestimate

Azotemia and Urinary Abnormalities CHAPTER 55 WBC, casts eosinophils Interstitial nephritis Abnormal urinalysis Red blood cells Renal artery or vein occlusion RBC casts Proteinuria Angiogram of GFR based on a creatinine-based eGFR; in that case, the cystatin C eGFR may be more accurate. APPROACH TO THE PATIENT Azotemia Once GFR reduction has been established, the physician must decide if it represents acute or chronic renal injury. The clinical circumstances, history, and laboratory data often make this an easy distinction. However, the laboratory abnormalities characteristic of chronic renal failure, including anemia, hypocalcemia, and hyper phosphatemia, are also often present in patients presenting with acute renal failure. Radiographic evidence of renal osteodystrophy (Chap. 322) can be seen only in chronic renal failure but is a very late finding, typically in patients with end-stage renal disease (ESRD) maintained on dialysis. The urinalysis and renal ultrasound can facilitate distinguishing acute from chronic renal failure. An approach to the evaluation of azotemic patients is shown in Fig. 55-1. Patients with advanced chronic renal insufficiency often have some protein uria, nonconcentrated urine (isosthenuria; isosmotic with plasma),

and small kidneys on ultrasound, characterized by increased echo genicity and cortical thinning. Treatment should be directed toward slowing the progression of renal disease and providing symptomatic relief for edema, acidosis, anemia, and hyperphosphatemia, as discussed in Chap. 322. Acute renal failure (Chap. 321) can result from processes that affect blood flow and glomerular perfusion (prerenal azotemia), intrinsic renal diseases (affecting small vessels, glomeruli, or tubules), or postrenal processes (obstruction of urine flow in ureters, bladder, or urethra) (Chap. 331). PRERENAL FAILURE Decreased renal perfusion accounts for 40–80% of cases of acute renal failure and, if appropriately treated, is readily reversible. The etiologies of prerenal azotemia include any cause of decreased circulating blood volume (gastrointestinal hemorrhage, burns, diarrhea, diuretics), volume sequestration (pancreatitis, peritonitis, rhabdomyolysis), or decreased effective arterial volume (cardio genic shock, sepsis). Renal and glomerular perfusion also can be affected by reductions in cardiac output from peripheral vasodi lation (sepsis, drugs) or profound renal vasoconstriction (severe heart failure, hepatorenal syndrome, agents such as nonsteroidal anti-inflammatory drugs [NSAIDs]). True or “effective” arterial hypovolemia leads to a fall in mean arterial pressure, which in turn triggers a series of neural and humoral responses, including activa tion of the sympathetic nervous and renin-angiotensin-aldosterone systems and vasopressin (AVP) release. GFR is maintained by pros taglandin-mediated dilatation of afferent arterioles and angiotensin II–mediated constriction of efferent arterioles. Once the mean arte rial pressure falls below 80 mmHg, GFR declines steeply. PART 2 Cardinal Manifestations and Presentation of Diseases Blockade of prostaglandin production by NSAIDs can result in severe vasoconstriction and acute renal failure. Blocking angioten sin action with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreases efferent arteriolar tone and in turn decreases glomerular capillary perfusion pres sure. Patients taking NSAIDs and/or ACE inhibitors/ARBs are most susceptible to hemodynamically mediated acute renal failure when blood

volume or arterial perfusion pressure is reduced for any reason; under these circumstances, preservation of GFR is dependent on afferent vasodilation due to prostaglandins and effer ent vasoconstriction due to angiotensin II. Patients with bilateral renal artery stenosis (or stenosis in a solitary kidney) can also be dependent on efferent arteriolar vasoconstriction for maintenance of glomerular filtration pressure and are particularly susceptible to a precipitous decline in GFR when given ACE inhibitors or ARBs. Prolonged renal hypoperfusion may lead to acute tubular necro sis (ATN), an intrinsic renal disease that is discussed below. The urinalysis and urinary electrolyte measurements can be useful in distinguishing prerenal azotemia from ATN (Table 55-2). The TABLE 55-2 Laboratory Findings in Acute Renal Failure OLIGURIC ACUTE RENAL FAILURE INDEX PRERENAL AZOTEMIA BUN/PCr ratio

> 20:1 10–15:1 Urine sodium UNa, meq/L <20 40 Urine osmolality, mosmol/L H2O 500 <350 Fractional excretion of sodiuma <1% 2% Urine/plasma creatinine UCr/PCr 40 <20 Urinalysis (casts) None or hyaline/granular Muddy brown = × × × FE U P

P U a Na Na Cr Na cr Abbreviations: BUN, blood urea nitrogen; PCr, plasma creatinine concentration; PNa, plasma sodium concentration; UCr, urine creatinine concentration; UNa, urine sodium concentration.

urine Na and osmolality of patients with prerenal azotemia can be predicted from the stimulatory actions of norepinephrine, angio tensin II, AVP, aldosterone, and low tubule fluid flow rate. In pre renal conditions, the tubules are intact, leading to a concentrated urine (>500 mosmol), avid Na retention (urine Na concentration, <20 mmol/L; fractional excretion of Na [FENa], <1%), and UCr/PCr

> 40 (Table 55-2). The FENa is typically >1% in ATN but may be <1% in patients with milder, nonoliguric ATN (e.g., from rhabdomyolysis) and in patients with underlying “prerenal” disorders, such as con gestive heart failure (CHF) or cirrhosis or hepatorenal syndrome. The prerenal urine sediment is usually normal or has hyaline and granular casts, whereas the sediment of ATN usually is filled with cellular debris, tubular epithelial casts, and dark (muddy brown) granular casts. Microscopic examination of a urine sediment is a key test in AKI, since the presence of dark granular casts and/or tubular epithelial cells in the urine is highly predictive of ATN. The measurement of urinary biomarkers associated with tubular injury is a promising technique to detect subclinical ATN and/or help further diagnose the exact cause of acute renal failure. POSTRENAL AZOTEMIA Urinary tract obstruction accounts for <5% of cases of acute renal failure but is usually reversible and must be ruled out early in the evaluation (Fig. 55-1). Since a single kidney is capable of adequate clearance, complete obstructive acute renal failure requires obstruc tion at the urethra or bladder outlet, bilateral ureteral obstruction, or unilateral obstruction in a patient with a

> single functioning kidney. Obstruction is usually diagnosed by the presence of ure teral and renal pelvic dilation on renal ultrasound. However, early in the course of obstruction or if the ureters are unable to dilate (e.g., encasement by pelvic or periureteral tumors or by retroperito neal fibrosis), the ultrasound examination may be negative. Other imaging, such as a furosemide renogram (MAG3 nuclear medicine study), may be required to better define the presence or absence of obstructive uropathy. The specific urologic conditions that cause obstruction are discussed in Chap. 331. INTRINSIC RENAL DISEASE When prerenal and postrenal azotemia have been excluded as etiologies of renal failure, an intrinsic parenchymal renal disease is present. Intrinsic renal disease can arise from processes involving large renal vessels, intrarenal microvasculature and glomeruli, or the tubulointerstitium. Ischemic and toxic ATN account for ~90% of cases of acute intrinsic renal failure. As outlined in Fig. 55-1, the clinical setting and urinalysis are helpful in separating the possible etiologies. Prerenal azotemia and ATN are part of a spectrum of renal hypoperfusion; evidence of structural tubule injury is pres ent in ATN, whereas prompt reversibility occurs with prerenal azotemia upon restoration of adequate renal perfusion. Thus, ATN often can be distinguished from prerenal azotemia by urinalysis and urine electrolyte composition (Table 55-2 and Fig. 55-1). Ischemic ATN is observed most frequently in patients who have undergone major surgery, trauma, severe hypovolemia, overwhelming sepsis, or extensive burns. Nephrotoxic ATN complicates the administra tion of many common medications, usually by inducing a combi nation of intrarenal vasoconstriction, direct tubule toxicity, and/ or tubular obstruction. The kidney is vulnerable to toxic injury by virtue of its rich blood supply (25% of cardiac output) and its ability to concentrate and metabolize toxins. A diligent search for hypo tension and nephrotoxins usually uncovers the specific etiology of ATN. Discontinuation of nephrotoxins and stabilization of blood pressure often suffice without the need for dialysis, with ongoing regeneration of tubular cells. An extensive list of potential drugs and toxins implicated in ATN is found in Chap. 321. Processes involving the tubules and interstitium can lead to acute kidney injury (AKI), a subtype of acute renal failure. These processes include drug-induced interstitial nephritis (especially by antibiotics, NSAIDs, and proton pump inhibitors), severe infections

(both bacterial and viral), systemic diseases (e.g., systemic lupus erythematosus), and systemic disorders (e.g., sarcoidosis, Sjögren’s syndrome, lymphoma, or leukemia). A list of drugs associated with allergic interstitial nephritis is found in Chap. 328. Urinalysis usu ally shows mild to moderate proteinuria, hematuria, and pyuria (~75% of cases) and occasionally WBC casts. The finding of RBC casts in interstitial nephritis has been reported but should prompt a search for glomerular diseases (Fig. 55-1). Renal biopsy will be needed to distinguish among these possibilities. The classic sediment finding in allergic interstitial nephritis is a predominance (>10%) of urinary eosinophils with Wright’s or Hansel’s stain; how ever, urinary eosinophils can be increased in several other causes of AKI, such that measurement of urine eosinophils has no diagnostic utility in renal

disease. This test is no longer recommended in the workup of AKI. Occlusion of large renal vessels, including arteries and veins, is an uncommon cause of acute renal failure. A significant reduc tion in GFR by this mechanism suggests bilateral processes or, in a patient with a single functioning kidney, a unilateral process. In patients with preexisting renal artery stenosis, a substantial renal collateral circulation can develop over time and sustain renal perfusion—typically not enough to sustain glomerular filtration, but enough to maintain tissue viability—in the event of total renal artery occlusion. Renal arteries can be occluded with atheroemboli, thromboemboli, in situ thrombosis, aortic dissection, or vasculitis. Atheroembolic renal failure can occur spontaneously but most often is associated with recent aortic instrumentation. The emboli are cholesterol-rich and lodge in medium and small renal arteries, with a consequent eosinophil-rich inflammatory reaction. Patients with atheroembolic acute renal failure often have a normal urinaly sis, but the urine may contain eosinophils and casts. The diagnosis can be confirmed by renal biopsy, but this procedure is often unnec essary when other stigmata of atheroemboli are present (livedo reticularis, distal peripheral infarcts, eosinophilia). Renal artery thrombosis may lead to mild proteinuria and hematuria, whereas renal vein thrombosis typically occurs in the context of heavy pro teinuria and hematuria. These vascular complications often require angiography for confirmation and are discussed in Chap. 329. Diseases of the glomeruli (glomerulonephritis and vasculitis) and the renal microvasculature (hemolytic-uremic syndromes, thrombotic thrombocytopenic purpura, and malignant hyperten sion) usually present with various combinations of glomerular injury: proteinuria, hematuria, reduced GFR, and alterations of sodium excretion that lead to hypertension, edema, and circulatory congestion (acute nephritic syndrome). These findings may occur as primary renal diseases or as renal manifestations of systemic dis eases. The clinical setting and other laboratory data help distinguish primary renal diseases from systemic diseases. The finding of RBC casts in the urine is an indication for early renal biopsy (Fig. 55-1), as the pathologic pattern has important implications for diagnosis, prognosis, and treatment. Hematuria without RBC casts can also be an indication of glomerular disease, since RBC casts are highly specific but very insensitive for glomerulonephritis. The specificity of urine microscopy can be enhanced by examining urine with a phase contrast microscope capable of detecting dysmorphic red cells (“acanthocytes”) that are associated with glomerular disease. This evaluation is summarized in Fig. 55-2. A detailed discussion of glomerulonephritis and diseases of the microvasculature is found in Chap. 328. OLIGURIA AND ANURIA Oliguria refers to a 24-h urine output <400 mL, and anuria is the complete absence of urine formation (<100 mL). Anuria can be caused by complete bilateral urinary tract obstruction; a vascular catastrophe (dissection or arterial occlusion); renal vein throm bosis; acute cast nephropathy in myeloma; renal cortical necrosis; severe ATN; severe rapidly progressive glomerulonephritis; com bined therapy with NSAIDs, ACE inhibitors, and/or ARBs; and

HEMATURIA Proteinuria (>500 mg/24 h), Dysmorphic RBCs or RBC casts Pyuria, WBC casts Urine culture Urine eosinophils Serologic and hematologic evaluation: blood cultures, anti-GBM antibody, ANCA, complement levels, cryoglobulins, hepatitis B and C serologies, VDRL, HIV, ASLO Azotemia and Urinary Abnormalities CHAPTER 55 Hemoglobin electrophoresis Urine cytology UA of family members 24 h urinary calcium/uric acid IVP +/– Renal ultrasound As indicated: retrograde pyelography or arteriogram, or cyst aspiration Renal biopsy Cystoscopy Urogenital biopsy and evaluation Renal CT scan Renal biopsy of mass/lesion Follow periodic urinalysis FIGURE 55-2 Approach to the patient with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; CT, computed tomography; GBM, glomerular basement membrane; IVP, intravenous pyelography; RBC, red blood cell; UA, urinalysis; VDRL, Venereal Disease Research

Laboratory; WBC, white blood cell. hypovolemic, cardiogenic, or septic shock. Oliguria is never nor mal, since at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load. Nonoliguria refers to urine output >400 mL/d in patients with acute or chronic azotemia. With nonoliguric ATN, disturbances of potassium and hydrogen balance are less severe than in oliguric patients, and recovery to normal renal function is usually more rapid. ABNORMALITIES OF THE URINE ■ ■PROTEINURIA The evaluation of proteinuria is shown schematically in Fig. 55-3 and typically is initiated after detection of proteinuria by dipstick examina tion. The dipstick measurement detects only albumin and gives falsepositive results at pH >7.0 or when the urine is very concentrated or contaminated with blood. Because the dipstick relies on urinary albu min concentration, a very dilute urine may obscure significant protein uria on dipstick examination. Quantification of urinary albumin on a spot urine sample (ideally from a first morning void) by measurement of an albumin-to-creatinine ratio (ACR) is helpful in approximating a 24-h albumin excretion rate (AER), where ACR (mg/g) ≈ AER (mg/24 h). Furthermore, proteinuria that is not predominantly due to albumin will be missed by dipstick screening. This information is particularly important for the detection of Bence-Jones proteins in the urine of patients with multiple myeloma. Tests to measure total urine protein concentration accurately rely on precipitation with sulfosalicylic or trichloroacetic acid (Fig. 55-3). As with albuminuria, the ratio of

PROTEINURIA ON URINE DIPSTICK Quantify by 24-h urinary excretion of protein and albumin or first morning spot albumin-to-creatinine ratio *Severely increased albuminuria 300–3500 mg/d or 300–3500 mg/g *Moderately increased albuminuria 30–300 mg/d or 30–300 mg/g PART 2 Cardinal Manifestations and Presentation of Diseases RBCs or RBC casts on urinalysis In addition to disorders listed under *moderately increased albuminuria consider Myeloma-associated kidney disease (check UPEP) Intermittent proteinuria Postural proteinuria Congestive heart failure Fever Exercise Consider Early diabetes Essential hypertension Early stages of glomerulonephritis (especially with RBCs, RBC casts) *Moderately and severely increased albuminuria were previously termed “microalbuminuria” and “macroalbuminuria,” respectively. FIGURE 55-3 Approach to the patient with proteinuria. Investigation of proteinuria is often initiated by a positive dipstick on routine urinalysis. Conventional dipsticks detect predominantly albumin and provide a semiquantitative assessment (trace, 1+, 2+, or 3+), which is influenced by urinary concentration as reflected by urine specific gravity (minimum, <1.005; maximum, 1.030). However, more exact determination of proteinuria should employ a spot morning protein/creatinine ratio (mg/g) or a 24-h urine collection (mg/24 h). FSGS, focal segmental glomerulosclerosis; RBC, red blood cell; UPEP, urine protein electrophoresis. protein to creatinine in a random “spot” urine can also provide a rough estimate of protein excretion; for example, a protein/creatinine ratio of 3.0 correlates to ~3.0 g of proteinuria per day. Formal assessment of urinary protein excretion requires a 24-h urine protein collection (see “Assessment of GFR,” above). The magnitude of proteinuria and its composition in the urine depend on the mechanism of renal injury that leads to protein losses. Both charge and size selectivity normally prevent virtually all plasma albumin, globulins, and other high-molecular-weight proteins from crossing the glomerular wall; however, if this barrier is disrupted, plasma proteins may leak into the urine (glomerular proteinuria; Fig. 55-3). Smaller proteins (<20 kDa) are freely filtered but are read ily reabsorbed by the proximal tubule. Typically, healthy individuals excrete <150 mg/d of total protein and <30 mg/d of albumin. However, even at albuminuria levels <30 mg/d, risk for progression to overt nephropathy or subsequent cardiovascular disease is increased. The remainder of the protein in the urine is secreted by the tubules (TammHorsfall, IgA, and urokinase) or represents small amounts of filtered

β2microglobulin, apoproteins, enzymes, and peptide hormones. Another mechanism of proteinuria entails excessive production of an abnormal protein that exceeds the capacity of the tubule for reabsorption. This situation most commonly occurs with plasma cell dyscrasias, such as multiple myeloma, amyloidosis, and lymphomas, that are associated with monoclonal production of immunoglobulin light chains. Other causes include lysozyme-associated nephropathy, a rare cause of kidney injury in patients with chronic myelomonocytic leukemia (CMML); overproduction of lysozyme results in excessive reabsorption of the enzyme by the proximal tubule, resulting in a severe tubulopathy with intracytoplasmic, membrane-bound vacuoles containing homogenous or granular electron dense material on electron microscopy. The normal glomerular endothelial cell forms a barrier composed of pores of ~100 nm that retain blood cells but offer little impediment to passage of most proteins. The glomerular basement membrane traps most large proteins (>100 kDa), and the foot processes of epithelial cells (podocytes) cover the urinary side of the glomerular basement

membrane and produce a series of nar row channels (slit diaphragms) to allow molecular passage of small solutes and water but not proteins. Some glomeru lar diseases, such as minimal change disease, cause fusion of glomerular epi thelial cell foot processes, resulting in predominantly “selective” (Fig. 55-3) loss of albumin. Other glomerular diseases can present with disruption of the base ment membrane and slit diaphragms (e.g., by immune complex deposition), resulting in losses of albumin and other plasma proteins. The fusion of foot pro cesses causes increased pressure across the capillary basement membrane, resulting in areas with larger pore sizes (and more severe “nonselective” protein uria) (Fig. 55-3). Nephrotic range

> 3500 mg/d or 3500 mg/g Go to Fig. 55-2 Nephrotic syndrome Diabetes Amyloidosis Minimal change disease FSGS Membranous glomerulopathy IgA nephropathy When the total daily urinary excretion of protein is >3.5 g, hypoalbuminemia, hyperlipidemia, and edema (nephrotic syndrome; Fig. 55-3) are often present as well. However, total daily urinary pro tein excretion >3.5 g can occur without the other features of the nephrotic syn drome in a variety of other renal diseases, including diabetes (Fig. 55-3). Plasma cell dyscrasias (multiple myeloma) can be associated with large amounts of excreted light chains in the urine, which may not be detected by dipstick. The light chains are filtered by the glomerulus and over whelm the reabsorptive capacity of the proximal tubule. Renal failure from these disorders occurs through a variety of mechanisms, including but not limited to proximal tubule injury, tubule obstruction (cast nephropathy), amyloid deposition, and light chain deposition (Chap. 328). The specific renal lesion is dictated by the sequence and structural characteristics of the monoclonal light chain; however, not all excreted light chains are nephrotoxic. Hypoalbuminemia in nephrotic syndrome occurs through excessive urinary losses and increased proximal tubule catabolism of filtered albumin. Edema results from renal sodium retention and reduced plasma oncotic pressure, which favors fluid movement from capillaries to interstitium. To compensate for the perceived decrease in effective intravascular volume, activation of the renin-angiotensin system, stim ulation of AVP, and activation of

> the sympathetic nervous system take place, promoting continued renal salt and water reabsorption and pro gressive edema. Filtered proteases, normally retained by the glomerular filtration barrier, can also directly activate sodium reabsorption by the epithelial Na channels in principal cells (ENaC) in nephrotic syndrome. Despite these changes, hypertension is uncommon in primary kidney diseases resulting in the nephrotic syndrome (Fig. 55-3 and Chap. 326). The urinary loss of regulatory proteins and changes in hepatic synthe sis contribute to the other manifestations of the nephrotic syndrome. A hypercoagulable state may arise from urinary losses of antithrombin III, reduced serum levels of proteins S and C, hyperfibrinogenemia, and enhanced platelet aggregation. Hypercholesterolemia may be severe and results from increased hepatic lipoprotein synthesis. Loss of immunoglobulins contributes to an increased risk of infection. Many diseases (some listed in Fig. 55-3) and drugs can cause the nephrotic syndrome; a complete list is found in Chap. 326. ■ ■HEMATURIA, PYURIA, AND CASTS Isolated hematuria without proteinuria, other cells, or casts is often indicative of bleeding from the urinary tract. Hematuria is defined as two to five RBCs per high-power field (HPF) and can be detected by dipstick. A false-positive dipstick for hematuria (where no RBCs are seen on urine microscopy) may occur when myoglobinuria is present,

often in the setting of rhabdomyolysis. Common causes of isolated hematuria include stones, neoplasms, tuberculosis, trauma, and pros tatitis. Gross hematuria with blood clots usually is not an intrinsic renal process; rather, it suggests a postrenal source in the urinary collecting system. Evaluation of patients presenting with microscopic hematuria is outlined in Fig. 55-2. A single urinalysis with hematuria is common and can result from menstruation, viral illness, allergy, exercise, or mild trauma. Persistent or significant hematuria (>3 RBCs/HPF on three urinalyses, a single urinalysis with >100 RBCs, or gross hematu ria) is associated with significant renal or urologic lesions in 9.1% of cases. The level of suspicion for urogenital neoplasms in patients with isolated painless hematuria and nondysmorphic RBCs increases with age. Neoplasms are rare in the pediatric population, and isolated hema turia is more likely to be “idiopathic” or associated with a congenital anomaly. Hematuria with pyuria and bacteriuria is typical of infection and should be treated with antibiotics after appropriate cultures. Acute cystitis or urethritis in women can cause gross hematuria. Hypercalci uria and hyperuricosuria are also risk factors for unexplained isolated hematuria in both children and adults. In some of these patients (50–60%), reducing calcium and uric acid excretion through dietary interventions can eliminate the microscopic hematuria. Isolated microscopic hematuria can be a manifestation of glo merular diseases. The RBCs of glomerular origin are often dysmor phic when examined by phase-contrast microscopy. Irregular shapes of RBCs may also result from pH and osmolarity changes produced along the distal nephron. Observer variability in detecting dysmorphic RBCs is common. The most common etiologies of isolated glomerular hematuria are IgA nephropathy, hereditary nephritis, and thin base ment membrane disease. IgA nephropathy and hereditary nephritis can lead to episodic gross hematuria. A family history of renal failure is often present in hereditary nephritis, and patients with thin base ment membrane disease often have family members with microscopic hematuria. A renal biopsy is needed for the definitive diagnosis of these disorders, which are discussed in more detail in Chap.

326. Hematuria with dysmorphic RBCs, RBC casts, and protein excretion >500 mg/d is virtually diagnostic of glomerulonephritis. RBC casts form as RBCs that enter the tubule fluid and become trapped in a cylindrical mold of gelled Tamm-Horsfall protein. Even in the absence of azotemia, these patients should undergo serologic evaluation and renal biopsy as outlined in Fig. 55-2. Isolated pyuria is unusual since inflammatory reactions in the kidney or collecting system also are associated with hematuria. The presence of bacteria suggests infection, and WBC casts with bacteria are indicative of pyelonephritis; “sterile pyuria” with negative urinary bacterial cultures can be seen in urogenital tuberculosis. WBCs and/or WBC casts also may be seen in acute glomerulonephritis as well as in tubulointerstitial processes such as interstitial nephritis and transplant rejection. Casts can be seen in chronic renal diseases. Degenerated cellular casts called waxy casts or broad casts (arising in the dilated tubules that have undergone compensatory hypertrophy in response to reduced renal mass) may be seen in the urine. ABNORMALITIES OF URINE VOLUME ■ ■POLYURIA By history, it is often difficult for patients to distinguish urinary fre quency (often of small volumes) from true polyuria (>3 L/d), and a quantification of volume by 24-h urine collection may be needed (Fig. 55-4). Polyuria results from two potential mechanisms: (1) excre tion of nonabsorbable solutes (such as glucose) or (2) excretion of water (usually from a defect in AVP production or renal responsiveness). To distinguish a solute diuresis from a water diuresis and to determine whether the diuresis is appropriate for the clinical circumstances, urine osmolality is measured. The average person excretes between 600 and 800 mosmol of solutes per day, primarily as urea and electrolytes. If the urine output is >3 L/d and the urine is dilute (<250 mosmol/L), total osmolar excretion is normal and a water diuresis is present. This circumstance could arise from polydipsia, inadequate secretion of AVP

POLYURIA (>3 L/24 h) Urine osmolality <250 mosmol

> “ 300 mosmol Solute diuresis Glucose, mannitol, radiocontrast, urea (from high protein feeding), medullary cystic diseases, resolving ATN, or obstruction, diuretics Azotemia and Urinary Abnormalities CHAPTER 55 Water deprivation test or ADH level History, low serum sodium Diabetes insipidus (DI) Central DI (vasopressin-sensitive) Posthypophysectomy, trauma, supra- or intrasellar tumor/cyst histiocystosis or granuloma, encroachment by aneurysm, Sheehan’s syndrome, infection, Guillain-Barré, fat embolus, empty sella Primary polydipsia Psychogenic Hypothalamic disease Drugs (thioridazine, chlorpromazine, anticholinergic agents) Nephrogenic DI (vasopressin-insensitive) Acquired tubular diseases: pyelonephritis, analgesic nephropathy, multiple myeloma, amyloidosis, obstruction, sarcoidosis, hypercalcemia, hypokalemia, Sjögren’s syndrome, sickle cell anemia Drugs or toxins: lithium, demeclocycline, methoxyflurane, ethanol, diphenylhydantoin, propoxyphene, amphotericin Congenital: hereditary, polycystic or medullary cystic disease FIGURE 55-4 Approach to the patient with polyuria. ADH, antidiuretic hormone; ATN, acute tubular necrosis. (central diabetes insipidus), or failure of renal tubules to respond to AVP (nephrogenic diabetes insipidus). If the urine volume is >3 L/d and urine osmolality is >300 mosmol/L, a solute diuresis is clearly present and a search for the responsible solute(s) is mandatory. Excessive filtration of a poorly reabsorbed solute such as glucose or mannitol can depress reabsorption of NaCl

and water in the proximal tubule and lead to enhanced excretion in the urine. Poorly controlled diabetes mellitus with glucosuria is the most common cause of a sol ute diuresis, leading to volume depletion and serum hypertonicity. Since the urine sodium concentration is less than that of blood, more water than sodium is lost, causing hypernatremia and hypertonicity. Common iatrogenic solute diuresis occurs in association with man nitol administration, radiocontrast media, and high-protein feedings (enteral or parenteral), leading to increased urea production and excretion. Less commonly, excessive sodium loss may result from cystic renal diseases or Bartter’s syndrome or may develop during a tubulointerstitial process (such as resolving ATN). In these so-called salt-wasting disorders, the tubule damage results in direct impairment of sodium reabsorption and indirectly reduces the responsiveness of the tubule to aldosterone. Usually, the sodium losses are mild, and the obligatory urine output is <2 L/d; resolving ATN and postobstructive diuresis are exceptions and may be associated with significant natri uresis and polyuria. Formation of large volumes of dilute urine is usually due to poly dipsic states or diabetes insipidus. Primary polydipsia can result from habit, psychiatric disorders, neurologic lesions, or medications. During

Revision #1
Created 2026-01-06 16:31:25 UTC by Omar Ayman
Updated 2026-01-06 16:31:26 UTC by Omar Ayman