INTRODUCTION

The urinalysis (UA) is critically important in the diagnosis of renal and urologic diseases (Akin et al., 1987; Kroenke et al., 1986). Indeed, it is generally the first test that the nephrologist looks at in evaluating acute kidney injury or chronic kidney disease (CKD). It would not be inaccurate to state that the UA is to nephrology what the electrocardiogram (EKG) is to cardiology (Sheets & Lyman, 1986). It is usually abnormal in patients with kidney disease and may reveal abnormalities in patients without proteinuria. If proteinuria is detected, it should be quantitated by a random urine albumin/creatinine and/or protein/creatinine ratio (see below and Chapter 2).

There are three portions of a complete UA: the appearance of the urine, the dipstick evaluation, and the microscopic examination. With a few exceptions (i.e., urine samples positive for glucose or ketones give a larger proportion of false negatives for leukocytes, and patients with clinically significant crystalluria will typically have negative dipsticks), a negative dipstick obviates the need to examine the sediment (Bonnardeaux et al., 1994; Schumann & Greenberg, 1979). However, with current automated UA techniques, both are often done in tandem.

APPEARANCE

The color of the urine should be assessed. The color of normal urine varies from clear (dilute) to yellow (concentrated). Macroscopic (gross) hematuria will make the urine appear red. Smoky red or cola-colored urine suggests glomerulonephritis. Dark yellow to orange urine is typical of bilirubinuria. Cloudy urine suggests pyuria or crystalluria (usually phosphates). Milky urine suggests chyluria (lymphatic/urinary fistula).

- Red urine
  - Dipstick positive for blood indicates heme is present
  - Red blood cells (RBCs) in urine sediment—hematuria
  - No RBCs in urine sediment—hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), lysis of RBCs in dilute and/or alkaline urine (suspect if specific gravity <1.010 and/or pH >8)
- Dipstick negative
  - Porphyria
  - Beet ingestion in susceptible patients (beeturia)
  - Food dyes
- Other colors
  - Orange—rifampin, phenazopyridine (Pyridium), carotene
  - Yellow—bilirubin
  - White—pyuria, chyluria, amorphous phosphate crystals
  - Green—methylene blue, amitryptiline, propofol, asparagus, Pseudomonas infection
  - Black—ochronosis (alkaptonuria), melanoma
DIPSTICK

- **Blood**
  - Dipstick positive for blood indicates heme is present (see above)
  - Microscopic hematuria by definition is hematuria in the absence of a visual change in color of the urine. As few as 2 to 3 RBC/hpf may make the dipstick positive
  - Heme pigments will make the dipstick positive in the absence of hematuria (see above)
  - Ascorbic acid may mask true hematuria (i.e., false negative dipstick)

- **pH**
  - Normal pH range is 4.5 to 8 (usually 5 to 7).
  - Low urine pH (<5.3)
    - High protein diet (increased endogenous acid production from sulfur-containing amino acids)
    - Metabolic acidosis (e.g., chronic diarrhea)
  - High urine pH (usually >7)
    - Metabolic alkalosis (e.g., vomiting)
    - Distal renal tubular acidosis (urine pH is >5.3 in face of acidosis)
    - Urea-splitting organisms (e.g., *Proteus*) (urine pH often ~9)
    - Urine that is infected will become alkaline over time due to formation of ammonia (NH₃) from bacterial urease
    - Urine that is exposed to air for a long time can also have elevated pH due to loss of CO₂ from the urine

- **Specific gravity**
  - Specific gravity is the weight of urine relative to distilled water and reflects the number and size (weight) of particles in urine. Osmolality is dependent only on the number of particles (solute concentration) in urine. Specific gravity is usually directly proportional to osmolality. However, iodinated contrast and, to a lesser extent, protein, will increase specific gravity but have little effect on osmolality. The normal range of urine specific gravity is 1.001 (very dilute) to 1.030 (very concentrated). Urine specific gravity of 1.010 is the same as plasma (isosthenuria). If specific gravity is not >1.022 after a 12-hour overnight fast (food and water), renal concentrating ability is impaired.
  - In an oliguric patient, a specific gravity >1.020 suggests normal ability to concentrate urine and prerenal failure (decreased renal blood flow), whereas ~1.010 suggests loss of tubular function (acute tubular necrosis/acute kidney injury).
  - In a hyponatremic patient, an inappropriately high specific gravity (>1.010) suggests antidiuretic hormone (ADH) secretion (see Chapter 4).
  - In a hypernatremic patient, an inappropriately low specific gravity (<1.010) suggests diabetes insipidus (central or nephrogenic) (see Chapter 4).

- **Protein**
  - The dipstick detects primarily albumin. Normal urine has no protein by dipstick, but occasionally very concentrated urine will be trace positive for protein in healthy individuals. A positive dipstick should lead to a quantitative measurement. Classically, this was done by a 24-hour collection, but as creatinine is excreted at a constant rate, a ratio of urine albumin to creatinine or protein to creatinine is sufficient in most patients.
  - *Albumin versus total protein* (Shihabi et al., 1991). Healthy subjects excrete up to 30 mg of albumin and 150 to 200 mg of total protein
per day (and on average 1,000 mg of creatinine per day). Thus, the normal urine albumin to creatinine ratio (UACR) is <30 mg per g and the normal urine protein to creatinine ratio (UPCR) is <150 to 200 mg per g. UACR of 30 to 300 mg per g is considered to be microalbuminuria and >300 mg per g overt albuminuria. UPCR >500 mg per g indicates overt proteinuria.

- Classically, sulfosalicyclic acid (SSA) was added to the urine to detect total protein. A discrepancy between the dipstick and SSA test (e.g., 1+ protein in dipstick and 4+ by SSA) suggested the presence of a paraprotein (e.g., myeloma protein) in the urine. A marked discrepancy between UACR and UPCR gives the same information.

- Glucose
  Normal urine does not contain glucose due to reabsorption of filtered glucose by the proximal tubule.
  - Glycosuria with elevated blood glucose—diabetes mellitus (Singer et al., 1989)
  - Glycosuria with normal blood glucose—renal glycosuria
    - Isolated
    - Associated with other proximal tubular dysfunction (phosphaturia, aminoaciduria, bicarbonaturia) (Fanconi syndrome). One should exclude multiple myeloma

- Ketones
  Normally, there are no ketones in the urine.
  - Ketonuria without ketoacidosis—starvation, low carbohydrate (Atkins) diet, isopropyl alcohol ingestion
  - Ketonuria with ketoacidosis—diabetic or alcoholic ketoacidosis.
    Note that in some patients with ketoacidosis, the dipstick may be negative due to reduction of acetoacetate to β-hydroxybutyrate

- Bilirubin
  Normally there is no bilirubin in the urine. If present, this suggests any of the following:
  - Hepatobiliary disease (failure to conjugate and/or excrete bilirubin into the gut)
  - Hemolysis (increased production of bilirubin from heme)

- Urobilinogen
  Bilirubin is secreted in bile into the gut, where it is metabolized by microorganisms into urobilinogen. Urobilinogen is then absorbed and partially excreted into the urine. In the presence of liver disease, urobilinogen can accumulate in plasma and appear in the urine. Bilirubin without urobilinogen in the urine suggests biliary obstruction.

- Leukocyte esterase
  This is an enzyme found in white blood cells (WBCs) and indicates the presence of pyuria.
  - Urinary tract infection (UTI)
  - Sterile pyuria (see below)

- Nitrite
  *Enterobacteria* convert urinary nitrate to *nitrite*, and therefore a positive test suggests UTI. Note that not all organisms make nitrite, so UTI may be present with a negative nitrite too.

**MICROSCOPIC EXAMINATION**

- RBCs
  Hematuria (see Chapter 3) (Fig. 1.1)
Chapter 1 / Urinalysis

- **WBCs**
  - Infection (Ditchburn & Ditchburn, 1990) or sterile pyuria. With sterile pyuria, one should exclude interstitial nephritis; other causes include nonbacterial infection, prostatitis, nephrolithiasis, and glomerulonephritis. Eosinophiluria suggests interstitial nephritis (Fig. 1.2).

- **Squamous epithelial cells**
  - Squamous epithelial cells from the skin surface or from the outer urethra can appear in urine. Their significance is that they represent possible contamination of the specimen.

- **Bacteria**
  - Indicate possible infection (Fig. 1.3)

- **Yeast**
  - Could be infection versus contamination. Presence of pseudomyecelia suggests infection. Risk factors include indwelling catheters, recent antibiotics, immunosuppression, and diabetes.
FIGURE 1.3 White blood cells and bacteria. (Image courtesy of Medcom, Inc.) (See Color Plate.)

- **Crystals**
  - Calcium oxalate—dihydrate: tetragonal (envelopes); monohydrate: dumbbells—can be seen in normal urine; in large amounts, suggests calcium oxalate kidney stones or ethylene glycol poisoning (which is metabolized to oxalate) (Fig. 1.4)
  - Calcium phosphate—form in alkaline urine—amorphous; in large amounts, suggests calcium phosphate kidney stones (seen in RTA)
  - Uric acid—form in acid urine—pleomorphic, yellow/brown; when in large amounts, suggests uric acid kidney stones or nephropathy (Fig. 1.5)
  - Cystine—hexagonal—indicates cystinuria (Fig. 1.4)

FIGURE 1.4 Calcium oxalate (*horizontal arrow*) and cystine (*vertical arrow*) crystals. (Image courtesy of Jessie Hano, M.D.) (See Color Plate.)
Magnesium ammonium phosphate (triple phosphate)—coffin-lids—suggests struvite stones (a urea-splitting organism must be present to produce NH$_3$ and elevate urine pH) (Fig. 1.6)

Casts

Urinary casts are formed in the distal convoluted tubule (DCT) or the collecting duct (distal nephron).

Hyaline casts are composed primarily of a mucoprotein (Tamm-Horsfall protein) secreted by tubule cells. They are formed in concentrated urine and can be seen in small numbers in healthy patients; large amounts suggest low urinary flow (prerenal or postrenal state) (Fig. 1.7).

RBC casts are indicative of glomerulonephritis, with leakage of RBCs from glomeruli, or severe tubular damage (rare) (Fig. 1.8).
- WBC casts indicate acute pyelonephritis or kidney inflammation (usually tubulointerstitial) (Fig. 1.9).
- Granular casts are nonspecific but indicate kidney disease (Fig. 1.10). Acute kidney injury (acute tubular necrosis or “ATN”) is characterized by pigmented granular (“muddy brown”) casts.
- Renal tubular epithelial cell casts are seen in acute and chronic kidney disease (Fig. 1.11).
- Broad waxy casts are seen in chronic kidney disease (Fig. 1.12).
- Fatty casts and oval fat bodies (lipid-laden macrophages) can be seen in nephrotic syndrome. Under polarizing light, characteristic “Maltese crosses” can be seen (Fig. 1.13).

**FIGURE 1.7** Hyaline cast. (Image courtesy of Medcom, Inc.) (See Color Plate.)

**FIGURE 1.8** Red blood cell cast. (Image courtesy of T.S. Ing, M.D.) (See Color Plate.)
FIGURE 1.9  White blood cell cast. (Image courtesy of Jessie Hano, M.D.) (See Color Plate.)

FIGURE 1.10  Granular cast. (Image courtesy of Medcom, Inc.) (See Color Plate.)

CLINICAL SYNDROMES SUGGESTED BY THE UA

- Normal UA with elevated creatinine:
  - Prerenal
  - Obstruction (postrenal)
  - Hypercalcemia
  - Multiple myeloma
  - Nephrosclerosis
  - Vasculopathies of medium-size vessels
    - Scleroderma
    - Cholesterol emboli
    - Polyarteritis nodosa
    - Ischemic nephropathy
FIGURE 1.11 Renal tubular epithelial cell cast. (Image courtesy of Medcom, Inc.) (See Color Plate.)

FIGURE 1.12 Broad waxy cast. (Image courtesy of Medcom, Inc.) (See Color Plate.)

- Hematuria/proteinuria
- Glomerulonephritis
- Small-vessel vasculitis
- Massive proteinuria
- Diabetes
- Amyloid
- Membranous nephropathy
- Minimal-change disease
- Focal and segmental glomerulosclerosis (FSGS)
A 40-year-old male with a history of intermittent abdominal pain, seizures, and psychosis complains of abdominal pain and cramping. He also complains of light sensitivity. He was out in the sun yesterday and developed blistering, redness, and swelling of the skin. He has been vomiting and complains of constipation. He has noted that his urine turned red. He also has muscle pain, muscle weakness, and pain in the arms, legs, and back. He has not eaten well for several days. Physical examination reveals blisters, erythema on forehead and upper extremities, and diffuse guarding and tenderness in the abdomen.

**Blood chemistry:**
- Sodium, 141 mmol/L
- Potassium, 4.6 mmol/L
- Chloride, 106 mmol/L
- Total CO₂, 25 mmol/L
- Urea nitrogen, 40 mg/dL (urea 14.3 mmol/L)
- Creatinine, 2.0 mg/dL (177 mcmol/L)
- Glucose, 80 mg/dL (4.4 mmol/L)

**Urinalysis:**
- Color, red
- pH, 6.0
- Specific gravity, 1.025
- Protein, negative
- Blood, negative
- Glucose, negative
- Ketones, 1+
- Bilirubin, negative
- Urobilinogen, negative
- Leukocyte esterase, negative
- Nitrite, negative
- WBC, 3/hpf
- RBC, 0/hpf
- Bacteria, negative

**Q:** Which of the following best explains this patient’s presentation?
1. Volume depletion
2. UTI
3. Porphyria
4. Hemolysis
5. Rhabdomyolysis
6. Starvation

A: The most prominent finding is that the color of the urine is red. However, the sediment is negative for RBCs and the dipstick is negative for blood, thus excluding hemoglobinuria or myoglobinuria. The urine specific gravity is high, suggesting volume depletion from vomiting. The renal failure is likely to be prerenal failure with an elevated urea nitrogen/creatinine ratio, mild hypernatremia, lack of proteinuria, and absence of symptoms of renal obstruction. Ketonuria is suggestive of recent lack of food intake. The absence of pyuria or bacteruria and negative leukocyte esterase and nitrite rules out urinary infection. Red urine in combination with the recurrent abdominal pain/cramps, sunburned rash, history of seizures, and history of psychosis suggests acute intermittent porphyria.

An 82-year-old male with a history of calcium oxalate kidney stones and cold agglutinin disease presents for evaluation after a fall in the bathroom. He has chronic bilateral knee and hip pain and could not get back up by himself. He stayed down on the floor for 6 hours and was found by the home health nurse who called an ambulance and brought him to the emergency room. He denies syncope or head trauma. He does complain of chronic abdominal pain, which his primary care physician attributes to irritable bowel syndrome and/or kidney stones. Medications include hydrochlorothiazide, potassium citrate, and acetaminophen. On examination, he has limited range of motion of the hips and knees with pain with extremes of range of motion. There is mild right upper quadrant tenderness. He has 3/5 strength of the lower extremities with intact sensation and generalized hyporeflexia.

Blood chemistry:
- Sodium, 138 mmol/L
- Potassium, 5.6 mmol/L
- Chloride, 102 mmol/L
- Total CO₂, 22 mmol/L
- Plasma Urea nitrogen, 30 mg/dL (Urea 10.7 mmol/L)
- Plasma Creatinine, 2.5 mg/dL (221 mcmmol/L)
- Glucose, 135 mg/dL (7.5 mmol/L)
- Total calcium, 8.0 mg/dL (2 mmol/L)
- Inorganic phosphorus, 5.5 mg/dL (1.8 mmol/L)

Complete Blood Count:
- White blood cells 10000/mm³
- Hemoglobin 9.0 g/dL (90 g/L)
- Hematocrit 30%
- Platelets 300000/mm³
- Antinuclear antibodies (ANA) 1:40
- Plasma haptoglobin 200 mg/dL (2 g/L) (normal)
- Creatine kinase (CK) 10000 U/L (normal < 200)
- Chest X-ray – broken R eleventh rib
- Renal Ultrasound – 2 mm stone in the right kidney, no hydronephrosis
Review of the medical record indicates that the plasma urea nitrogen and creatinine were 10 mg per dL (3.6 mmol/L) and 0.8 mg per dL (71 mcmol/L) 1 month previously.

Q: Which of the following urinalyses is most consistent with the above patient?

1. Color, yellow  
   pH, 5.5  
   Specific gravity, 1.025  
   Protein, 2+  
   Blood, 1+  
   Glucose, negative  
   Ketones, 1+  
   Bilirubin, negative  
   Urobilinogen, negative  
   Leukocyte esterase, negative  
   Nitrite, negative  
   WBC, 2/hpf  
   RBC, 10/hpf  
   Bacteria, negative

2. Color, yellow  
   pH, 5.0  
   Specific gravity, 1.025  
   Protein, negative  
   Blood, 1+  
   Glucose, negative  
   Ketones, 1+  
   Bilirubin, negative  
   Urobilinogen, negative  
   Leukocyte esterase, negative  
   Nitrite, negative  
   WBC, 2/hpf  
   RBC, 2/hpf  
   Bacteria, negative  
   Calcium oxalate crystals present

3. Color, yellow  
   pH, 5.5  
   Specific gravity, 1.025  
   Protein, 1+  
   Blood: 4+  
   Glucose, negative  
   Ketones, 1+  
   Bilirubin, 2+  
   Urobilinogen, 2+  
   Leukocyte esterase, negative  
   Nitrite, negative  
   WBC, 2/hpf  
   RBC, 2/hpf  
   Bacteria, negative

4. Color, yellow  
   pH, 5.0  
   Specific gravity, 1.025  
   Protein, 1+  
   Blood, 4+  
   Glucose, negative  
   Ketones, 1+  
   Bilirubin, negative  
   Urobilinogen, negative  
   Leukocyte esterase, negative  
   Nitrite, negative  
   WBC, 3/hpf  
   RBC, 0/hpf  
   Bacteria, negative

A: The patient has acute renal failure and red urine. It is thus possible that he has glomerulonephritis. Option 1 is consistent with glomerulonephritis, as the prominent finding in this UA is the combination of proteinuria and hematuria. The ANA is positive, which seems consistent with nephritis associated with systemic lupus erythematosus or another collagen-vascular disease. However, a weakly positive ANA is frequently seen in the elderly and is unlikely to be meaningful.

Because of the history of nephrolithiasis and right upper quadrant pain, kidney stones are also a possibility. Option 2 is consistent with kidney stones; here, the UA lacks proteinuria and has hematuria in combination with calcium oxalate crystals. However, there is only a 2-mm parenchymal kidney stone without hydronephrosis, which is unlikely to explain this patient’s abdominal pain. The pain is more likely caused by a fractured rib as detected on the chest X-ray. He has chronic abdominal pain as well.
Hemolysis is another possibility. The patient has a history of cold agglutinin disease which can render RBCs susceptible to lysis mediated by complement. Option 3 is consistent with hemolysis since there is bilirubinuria, urobilinogenuria, and heme-positive urine consistent with hemoglobinuria. With hemolysis, the released hemoglobin binds haptoglobin; hence, plasma haptoglobin is reduced. However, in this patient, it is not low.

This case is most consistent with rhabdomyolysis. The patient had a fall and was unable to get up for 6 hours. This trauma and immobility is sufficient for significant muscle breakdown to occur. The plasma CK is high, which is consistent with rhabdomyolysis. There is also diffuse weakness in the lower extremities due to muscle breakdown. Rhabdomyolysis is also characterized by hyperkalemia and hyperphosphatemia as these substances are released from damaged muscle cells, both of which are present in this patient. The UA has large blood without hematuria (consistent with the presence of myoglobin, which is a heme pigment).

References