11

THE KIDNEYS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Describe the normal physiology of the kidneys
- Differentiate the renal handling of urea and creatinine
- Describe clinical situations where blood urea nitrogen and serum creatinine are elevated
- Describe the evolving role of cystatin C in estimating glomerular filtration rate
- Describe the limitations in the usefulness of the serum creatinine concentration in estimating kidney function
- Understand the clinical utility of the Cockcroft-Gault equation, the Modification of Diet in Renal Disease equation, and the Chronic Kidney Disease Epidemiology Collaboration equations to assess kidney function
- Determine creatinine clearance given a patient's 24-hour urine creatinine excretion and serum creatinine
- Estimate creatinine clearance given a patient's height, weight, sex, age, and serum creatinine and identify limitations of the methods for estimation of kidney function
- Understand the classification of chronic kidney disease, glomerular filtration rate categories, and albuminuria as predictors of disease

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Through the excretion of water and solutes, the kidneys are responsible in large part for maintaining homeostasis within the body. They also function in the activation and synthesis of many substances that affect blood pressure (BP), mineral metabolism, and red blood cell (RBC) production. The purpose of this chapter is to provide insight to the interpretation of laboratory tests in the assessment of kidney function, as well as provide an overview of the interpretation of a urinalysis.

KIDNEY PHYSIOLOGY

The functional unit of the kidneys is the nephron (**Figure 11-1**), and each of the two kidneys contains about 1 million nephrons. The major components of the nephron include the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct. Blood is delivered to the glomerulus, the filtering portion of the nephron, via the afferent arteriole. Acting as microfilters, the pores of glomerular capillaries allow substances with a molecular weight of up to 40,000 daltons to pass through them. Plasma proteins, such as albumin (mw 65,000 daltons) and RBCs do not normally pass through the glomerulus. Ionic charge also affects filtration as the glomerulus selectively retains negatively charged proteins such as albumin. In kidney disease involving the glomerulus, the effect of ionic charge becomes less discriminate and albuminuria develops. Most drugs are small enough to be freely filtered at the glomerulus, with the exception of large proteins and drugs bound to plasma proteins.[1]

The proximal tubule reabsorbs large quantities of water and solute. Sodium passively follows the reabsorption of water back into the blood. Glucose, uric acid, chloride, bicarbonate, amino acids, urea, hydrogen, phosphate, calcium, and magnesium also are primarily reabsorbed by the proximal tubule. Sodium, chloride, magnesium, and water are further reabsorbed in the loop of Henle. The distal tubule controls the amounts of sodium, potassium, bicarbonate, phosphate, and hydrogen that are excreted, and the collecting duct regulates the amount of water in the urine as a result of the effect of antidiuretic hormone (ADH), which facilitates water reabsorption.[1]

As shown in Figure 11-1, substances can enter the nephron from the peritubular blood or interstitial space via secretion. In addition, substances can be reabsorbed from primarily the distal tubule back into the systemic circulation via the peritubular vasculature. Tubular secretion occurs via two primary pathways in the proximal tubule: the organic acid transport system and the organic cation transport (OCT) system. Although each system is somewhat specific for anions and cations, respectively, some drugs such as probenecid are secreted by both pathways. Creatinine enters the tubule primarily by filtration through the glomerulus. However, a small amount of creatinine is also secreted by the OCT system into the proximal tubule. This becomes important when using the renal clearance of creatinine to estimate kidney function.[1]

Blood flow to the kidneys is determined, in large part, by cardiac output with about 20% or 1.2 L/min directed to the kidneys. Renal plasma flow (RPF) is directly related to renal blood flow (RBF) by taking the patient's hematocrit into consideration as follows:

$$\mathrm{RPF} = \mathrm{RBF} \times (1 - \mathrm{Hct}) \qquad (1)$$

OBJECTIVES

- Describe the role of the pharmacist in the care of patients with acute or chronic kidney disease
- Discuss the various components assessed by macroscopic, microscopic, and chemical analysis of the urine
- Describe the role of commonly obtained urinary electrolytes and the fractional excretion of sodium in the diagnostic process

where RPF = renal plasma flow; RBF = renal blood flow; and Hct = hematocrit. The normal value for RPF is about 625 mL/min. Of the plasma that reaches the glomerulus, about 20% is filtered and enters the proximal tubule, resulting in a glomerular filtration rate (GFR) of about 125 mL/min. The GFR is often used as a measure of the degree of kidney excretory function in a patient. The kidneys filter about 180 L of fluid each day; of this amount, they excrete only 1.5 L as urine. Thus, more than 99% of the initial glomerular filtrate is reabsorbed back into the bloodstream. Many solutes, such as creatinine and many renally eliminated drugs, are concentrated in the urine.[1]

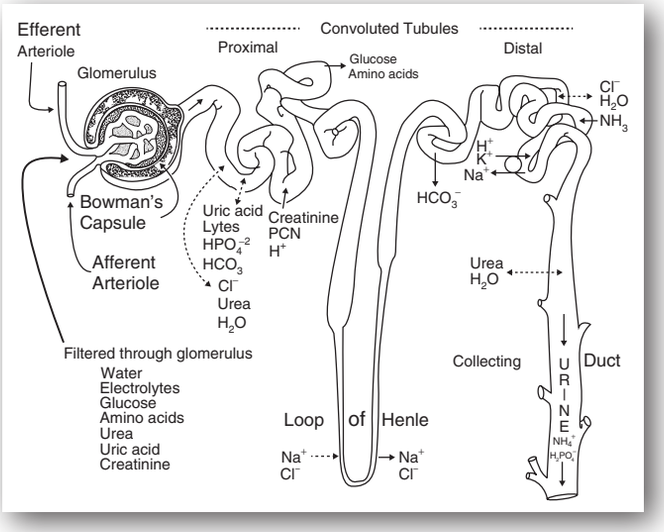

FIGURE 11-1. The nephron. Arrows pointing toward the nephron represent substances entering from the peritubular blood or interstitial space. Arrows heading away represent reabsorption. Solid arrows represent an active (energy-requiring) process, and dashed arrows represent a passive process. PCN = penicillin; lytes = electrolytes. *Source*: Reprinted from Inker LA, Astor BC, Fox CH et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014; 63:713-35. Copyright ©2014, with permission from Elsevier.

DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE

The classification of ***chronic kidney disease*** (CKD) is based on the nature or cause of the abnormality (structure, function), the GFR category (g1 through g5), and albuminuria category (a1 through a3). The prognostic categories can be found at http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.[2] CKD has been defined as GFR <60 mL/min/1.73 m^2 for greater than three months.[2] The use of estimating equations (eGFR) or the measurement of GFR rather than using serum creatinine (SCr) or cystatin C alone can provide the basis for the classification of kidney function. Additionally, markers of kidney damage such as albuminuria (albumin excretion rate >30 mg/24 hr, albumin-to-creatinine [ACR] ratio 30 mg/g), structural (e.g., polycystic kidney disease, hydronephrosis, renal artery stenosis), or functional anomalies (e.g. urinary sediment such as casts or renal tubular disorders) are used for prognosis of risk: low risk (no markers of kidney disease), moderately increased risk, high risk, and very high risk.[2] This information is useful to guide therapy and further monitoring of and CKD complications.

ASSESSMENT OF KIDNEY FUNCTION

Classification of kidney disease as well as dosing of medications depends on an accurate and reliable method of assessing kidney function.[2] Direct measurement of GFR using markers such as inulin and iothalamate is the most accurate assessment of kidney function but is not used routinely in clinical practice due to cost and practical concerns. Measurements of timed 24-hour urine creatinine (UCr) collections are difficult by design, flawed by collection errors, and used only when determination of GFR is vital and the use of the eGFR equations are not reliable. The estimation of creatinine clearance (CrCl) through equations such as Cockcroft-Gault has been the "gold standard" for drug dosing. Recently, serum concentrations of cystatin C, an endogenous amino acid, have been evaluated as an alternative method to predict GFR in children as well as adults.[3-5] eGFR had been initially validated using the Modification of Diet in Renal Disease (MDRD) equation and was used to stage and monitor CKD until recently.[6-10] The CKD Epidemiology Creatinine Equation 2009 is now currently recommended to estimate GFR.[2] Recently, the U.S. Food and Drug Administration (FDA) Guidance to Industry draft revision has proposed that both the eGFR and CrCl be incorporated into the package insert dosage recommendations for patients with decreased renal function.[11] With more clinical laboratories reporting eGFR values and as pharmacokinetic data reference both eGFR and CrCl for new medications, the use of eGFR to adjust medication doses may become more commonplace.