APPROACH TO THE PATIENT WITH RENAL DISEASE

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LEARNING OBJECTIVES

- List the components of the history and physical examination that can used to differentiate pre-renal from intrinsic renal disease
- Given a patient with decreased renal function, list the laboratory tests, radiographic findings, and other tools that can be used to assess duration of renal disease
- Identify the pattern of abnormalities present in each of the major renal disease syndromes
- Distinguish between and outline the strength and weaknesses of the imaging studies used in the evaluation of patients with renal disease

GLOSSARY

ADH antidiuretic hormone
AIN acute interstitial nephritis
ANCA *acronym* anti-neutrophil cytoplasmic antibody
anuria less than 100 ml urine/24 hours
ARF acute renal failure
ATN acute tubular necrosis **bacteriuria** bacteria in the urine **BUN** blood urea nitrogen
cANCA diffuse cytoplasmic staining of anti-neutrophil cytoplasmic antibody
CRF chronic renal failure
EABV effective arterial blood volume
ECF extra-cellular fluid
EDTA ethylene diamine tetra-acetate (chelating agent) **ELISA** *acronym* enzyme-linked immunosorbent assay **ESRD** end-stage renal disease
FGS focal glomerulosclerosis
GBM glomerular basement membrane
GFR glomerular filtration rate
GN glomerulonephritis
gp330 glycocprotein Mr 330 kD, multiligand endocytic receptor of the LDL receptor gene family, same as *megalin*
HCV hepatitis C virus (antigen-antibody complex-associated glomerulonephritis)
hematuria blood (red cells) in the urine
IDDM insulin-dependent diabetes mellitus
KUB kidney - ureter - bladder, plain xray of the abdomen to assess urinary tract
MCD minimal change disease (also called "nil disease" or lipoid nephropathy)
megalin multiligand endocytic receptor of the LDL receptor gene family, same as gp330; main antigenic target in passive Heymann nephritis
MN membranous nephropathy
MPGN membranoproliferative glomerulonephritis
nephritis nephritic *adj.* inflammation of the kidney, from the Greek *nephros* kidney
nephrosis any disease of the kidney
nephrotic *adj.* caused by nephrosis, "nephrotic syndrome" reserved for marked proteinuria (5 gm/d) together with a constellation of associated findings

NIDDM non-insulin dependent diabetes mellitus
non-oliguria more than 400 ml urine/24 hours
NSAID *acronym* (en-said) non-steroidal anti-inflammatory drug
oliguria less than 400 ml urine/24 hours
pANCA perinuclear anti-neutrophil cytoplasmic antibody (cANCA = diffuse cytoplasmic staining)
polyarteritis *disease* multiple sites of inflammatory and destructive lesions in the arterial system, also called *periarteritis nodosa*
PTH parathyroid hormone
pyuria white cells in the urine
RPF renal plasma flow
RPGN rapidly progressive glomerulonephritis
RTA renal tubular acidosis
SLE systemic lupus erythematosus
SSA sulfosalicylic acid (in test for all urinary proteins, not just albumin)
Tamm-Horsfall *protein* normally produced by renal tubules, constituent of casts; Igor *Tamm*, American virologist, born 1922; Frank Lappin *Horsfall*, Jr., American virologist, 1906-1971
TIN (chronic) tubulointerstitial nephritis

I. Introduction

Diseases of the kidney can present as a variety of clinical syndromes. In some cases, the clinical presentation is directly referable to the kidney, as with the finding of proteinuria or an increased serum creatinine concentration. In other instances, the presentation reflects the impact of impaired renal function on other organ systems, such as edema or shortness of breath resulting from renal salt retention. Still other patients are asymptomatic and are simply found to have an abnormal urinalysis on routine examination. Utilizing a systematic approach to the patient with renal disease will enhance the likelihood that an accurate diagnosis can be made.

First, the clinician should determine the duration of the disease. Second, renal function should be measured, to determine whether the patient has suffered a loss in renal function and, if so, to what degree. Third, the specific renal syndrome should be identified, on the basis of information obtained through the history and physical examination, routine laboratory testing, and imaging of the kidneys. Assessment of volume status deserves particular attention because volume abnormalities are common in patients with renal disease and offer an important clue not only to the presence of renal failure but also to its management. Approaching the patient in this manner will allow the clinician to establish the correct diagnosis, and at the same time, accurately determine disease duration and severity, and institute appropriate therapy.

Key features of the history and physical exam that support a pre-renal vs intrinsic renal cause of kidney dysfunction are shown below in Table 1.

Table 1: **Features of History and Physical Examination that Help Differentiate Pre-renal from Intrinsic Kidney Failure**

Database	History	Physical Examination
Pre-renal	Vomiting, diarrhea Blood loss, Increased thirst	Orthostatic hypotension Decreased skin turgor Dry mucous membranes Low jugular venous pressure
Intrinsic renal	Increased urination Dyspnea, edema Nocturia, hematuria Renal stones	Hypertension Retinopathy Elevated jugular venous pressure Rales, S3, peripheral edema

II. Determining Disease Duration

Determining whether kidney disease is acute or chronic is important both in asymptomatic patients with normal renal function and in patients with clinical evidence of renal insufficiency. There are two main reasons to differentiate acute from chronic kidney disease. First, acute kidney disease is more likely to be self-limited and therefore have a better prognosis. Second, the treatment of renal disease may vary, depending on whether the disease is of recent onset or is long-standing. This is particularly true for treatment of acute kidney injury versus treatment for chronic kidney disease. There are specific therapies for certain types of acute kidney disease that do not apply to chronic kidney disease and such therapy may prevent acute kidney failure from becoming chronic.

Several tools can help determine disease duration. Use of old medical records is particularly valuable in dating the onset of an increased serum creatinine concentration, proteinuria, or hematuria. In patients with impaired renal function, measurement of kidney size by renal sonography or plain film of the abdomen is quite useful. Small kidneys (i.e., less than 8 cm in total length, in an adult), are an almost certain sign of chronic kidney disease. On the other hand, if the kidneys are normal in size, one cannot be certain whether the patient has acute or chronic renal disease. Radiographic evidence of renal osteodystrophy strongly supports the diagnosis of chronic kidney disease. The most precise way to differentiate acute kidney disease from chronic kidney disease is to perform a renal biopsy; however, this is not practical or necessary in most cases. Renal biopsy is useful when kidney size is normal on ultrasound or plain films of the abdomen (KUB: kidneys, ureters, and bladder view), but the history and physical examination and other clinical signs are unable to make a clear distinction between acute and chronic.

III. Assessment of Renal Function

Once kidney disease is discovered, the presence or degree of renal dysfunction should be determined. The glomerular filtration rate (GFR) is generally considered the best measure of renal function. Serial assessment of GFR can allow the clinician to determine the course of the underlying disease by demonstrating either rapid or slow rates of decline in renal function. Accurate determination of renal function also helps the clinician to make adjustments in the dosing of pharmacologic agents so as to prevent the accumulation of drugs and metabolites and, thereby, potential toxicities.

A. Serum Creatinine

Measurement of the serum creatinine concentration is the most commonly used method for determining the level of renal function. The creatinine concentration can be used to estimate GFR because creatinine varies inversely with the level of renal function. Normal creatinine concentrations range from 0.6 to 1.0 mg/dl in women and 0.8 to 1.3 mg/dl in men.

The major limitation of the serum creatinine level is its insensitivity to mild to moderate reductions in renal function. The relationship between creatinine level and GFR is nonlinear. A change in creatinine from 0.6 mg/dl to 1.2 mg/dl reflects a decline in GFR of approximately 50%. If a previous baseline value for creatinine does not exist for comparison, a creatinine of 1.2 would not draw clinical attention to a potential reduction of GFR. On the other hand, nephrologists are often consulted emergently when a patient's creatinine concentration rises from 5 mg/dl to 8 mg/dl, which is far less critical, because GFR has fallen from approximately 20 ml/min to 15 ml/min, a 25% decline. Nevertheless, it is important to detect changes in GFR at relatively low creatinine values, when renal injury may still be reversible.

Changes in the serum creatinine concentration are also slow to reflect acute changes in renal function because accumulation of creatinine in the blood and achievement of a new steady state occur gradually. For example, if acute kidney disease occurs and the GFR suddenly falls from 100 ml/min to 10 ml/min, the serum creatinine would not rise correspondingly for several days. In the absence of muscle breakdown, the creatinine rises by an amount equal to production.

B. Creatinine Clearance

A more accurate way to assess the GFR is with a 24-hour urine collection to determine the creatinine clearance. Creatinine is an endogenous marker of filtration that is produced at a relatively constant rate. Creatinine clearance (CCr) may be calculated by the following equation:

CCr (ml/min) = urine creatinine (mg/dl) × urine volume (ml/min) / plasma creatinine (mg/dl) × 1,440 Normal CCr is approximately 95 ± 20 ml/min in women and 125 ± 25 ml/min in men.

Creatinine is freely filtered and is not reabsorbed; it is thus excreted primarily by filtration. A small percentage of urinary creatinine is derived from tubular secretion via an organic acid pump in the proximal tubule. In the setting of normal renal function this small secretory component does not appreciably alter the close relationship between CCr and GFR. However, with loss of renal function, the percent of creatinine reaching the final urine via tubular secretion progressively increases. As a result, there is a tendency for the CCr to overestimate GFR in patients with chronic kidney disease.

In addition to the variability in tubular secretion, the reliability of CCr to assess renal function is diminished by the inability of most patients to accurately collect timed urine samples. The accuracy of the urine samples can be estimated on the basis of the normal daily rate of creatinine excretion: 15 to 20 mg/kg lean body weight in women and 20 to 25 mg/kg lean body weight in men. A creatinine excretion rate that is significantly less than the normal daily rate usually indicates an incomplete urine collection while an excretion rate significantly above the normal daily rate indicates over collection. Prolonged storage of urine can also invalidate urinary creatinine clearance measurements because high temperatures and low pH promote the conversion of creatine to creatinine in urine.

To avoid the inaccuracies and inconvenience of timed urine collections, the creatinine clearance can be estimated at the bedside by using the patient's age and PCr, which correlate inversely with GFR, and the patient's ideal body weight (IBW), which correlates directly with GFR:

$$\text{Estimated CCr} = (140 - \text{age}) \times (\text{IBW in kg}) / (72 \times \text{PCr})$$

When this equation is used for estimating CCr in women, the results should be multiplied by 0.85. This equation provides a quick and reasonably accurate estimate of GFR at the bedside and is particularly useful in determining dosage adjustments for pharmacologic agents excreted by the kidney.

The most common way that GFR is estimated is through the use of equations that account for age, race, sex, and serum creatinine. An equation, derived from the Modification of Diet in Renal Disease study, is now commonly used to more accurately assess renal function:

$$\text{GFR} = 170 \times [\text{Scr}]^{-0.999} \text{ x } [\text{age}]^{-0.176} \text{ x } [0.762 \text{ if female}] \times [1.180 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \text{ x } [\text{albumin}]^{0.318}$$

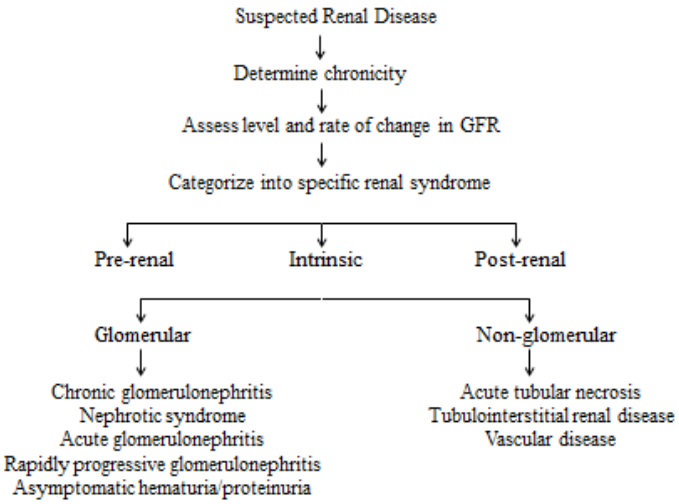
Modifications of the MDRD equation continue to be made to enhance the accuracy of the estimation. These equations estimate GFR rather than creatinine clearance and factor in ethnicity, gender, and serum albumin concentration. A GFR calculator that uses the most up to date equation is available on the internet site: www.kidney.org.

C. Inulin Clearance

Inulin is a fructose polymer that is freely filtered by the glomerulus and is neither reabsorbed nor secreted by the tubule. Thus, inulin clearance (CIn) is one of the most accurate methods of quantifying renal function. CIn can be determined by the following equation:

CIn (ml/min) = urine inulin (mg/dl) × urine volume (ml/min) / plasma inulin (mg/dl)

Inulin is an exogenous compound and must therefore be administered as a continuous infusion to achieve steady- state concentrations in the blood. The need for continuous infusion, the cost, and limited supply of inulin, prevent the routine clinical implementation of inulin-clearance testing.



After determining chronicity and current level of renal function, the clinician should attempt to classify the patient's renal disease into one of several syndromes, on the basis of the renal structures most affected. This classification is based on the history, physical examination, laboratory tests, and selected imaging studies. It is particularly important to identify prerenal and post-renal disorders because these entities are often readily reversible.

IV. Urinalysis in the Diagnosis of Renal Disease

Although the history and physical examination often provide important clues, the major non-invasive diagnostic tool available to the clinician is the urinalysis. Examination of the urine can also give some information about disease severity. In glomerular disease, for example, the presence of marked hematuria, red cell casts, and heavy proteinuria generally represents more severe disease than isolated hematuria or proteinuria alone.

Such a direct relationship between the urinalysis and severity is not always present. In a patient with acute glomerulonephritis, normalization of the urinalysis represents resolution of the active inflammatory process.

However, this change can reflect either recovery or healing with irreversible glomerular scarring and nephron loss. Distinguishing between these possibilities cannot always be achieved by measurement of the plasma creatinine concentration, since the total GFR and therefore the plasma creatinine concentration may remain stable with progressive disease due to hypertrophy of and hyperfiltration in the less affected glomeruli. In this setting, which has been best described after immunosuppressive therapy in lupus nephritis, repeat renal biopsy may be required to accurately estimate the status of the renal disease.

Performance of urinalysis: Despite these potential limitations, a complete urinalysis should be performed in all patients with renal disease. The specimen should be examined within 30 to 60 minutes of voiding; a midstream specimen is adequate in men, but the external genitalia must first be cleaned in women to avoid contamination with vaginal secretions. The urine should be centrifuged at 3000 rpm for 3 to 5 minutes, and the supernatant then poured into a separate tube.

A small amount of sediment should be placed on a slide for microscopic examination, while the supernatant should be tested for protein, glucose, heme pigments, and concentration.

Detection of protein: The urine dipstick detects negatively charged proteins and was designed to screen for albuminuria. Patients with increased excretion of cationic non-albumin proteins in the urine (most often immunoglobulin light chains in multiple myeloma) will have a negative or trace dipstick. In this setting, testing the urine with sulfosalicylic acid (SSA) will detect all proteins. A negative dipstick and a strongly positive SSA test are highly suggestive of excretion of a cationic protein as in myeloma kidney in an adult with acute renal failure and a bland (no to little cellularity) urine sediment.

Urinalysis Patterns

The value of the urinalysis lies in the association between different patterns of urinary findings and different renal disease syndromes (Table 2).

Table 2. Urinalysis findings and selected features of renal disease syndromes

Renal Disease	Urinalysis	Other features
Prerenal	SG: 1.020, glucose negative, protein negative, occasional hyaline casts	Signs and symptoms of decreased renal blood volume, congestive heart failure
Postrenal	SG: 1.007, protein negative, blood negative, 0-3 erythrocytes/hpf, 0-3 leukocytes/hpf	Decreased urine flow, symptoms of prostatism in men
Acute tubular necrosis	SG: 1.010, protein trace, blood negative, 1-3 leukocytes/hpf, many *pigmented granular casts*, 5-10 renal tubular casts/hpf, occasional renal tubular cells	History of hypotension, sepsis, administration of nephrotoxins such as radiocontrast, aminoglycosides, cisplatin exposure
Nephrotic syndrome	SG: 1.015, protein 4+, oval fat bodies, fatty casts	Edema, hypoalbuminemia
Acute tubulointerstitial nephritis	SG: 1.012, protein 1+, blood 2+, 20-30 leukocytes/hpf, + stain for *eosinophils*, few *leukocyte casts*, 1-15 erythrocytes/hpf	Fever, morbilliform rash, eosinophilia, recent administration of antibiotic
Chronic tubulointerstitial nephritis	SG: 1.012, protein 1+, glucose 1+ with normal serum glucose, 10-15 leukocytes/hpf, no bacteria	Type IV renal tubular acidosis, anemia, Na^+ wasting
Acute glomerulonephritis	SG: 1.020, 2+ protein, 3+ blood, 15-20 erythrocytes/hpf, 3-5 *erythrocyte casts*/hpf, 0-3 leukocytes/hpf	Recent upper respiratory tract infection, nephritic syndrome
Rapidly progressive glomerulonephritis	Same as acute glomerulonephritis	Nephritic syndrome, hemoptysis, rapid loss of renal function

V. Imaging Techniques for the Genitourinary System

Selected use of imaging studies can be an effective tool in the initial evaluation of patients with renal disease. Renal ultrasonography provides information on kidney size, structure, and symmetry; cortical thickness; and the presence of hydronephrosis and nephrolithiasis. At the same time, ultrasound avoids the nephrotoxicity of large-volume radiocontrast procedures, such as the intravenous pyelogram. A plain film of the abdomen (KUB) can be used to assess kidney size and detect calcifications indicative of renal stones or nephrocalcinosis. Magnetic resonance imaging of the genitourinary tract is also a useful, noninvasive imaging modality. In addition to providing a detailed structural image of the kidney, ureters, and bladder, MRI can be used to assess the renal vasculature. Magnetic resonance angiography, in which a gadolinium-based (non-iodine-containing) contrast agent is given intravenously, can be used in the evaluation of renovascular disease. This approach avoids the nephrotoxicity of the iodinated contrast used in conventional angiography. MRI is also an effective tool to detect renal vein thrombosis. Table 3 summarizes the use of the most commonly utilized imaging techniques used in the evaluation of patients with renal disease.

Table 3. Imaging studies used in approaching a patient with renal disease

Imaging study	Use
Plain radiograph of abdomen (KUB)	Determining kidney size and shape Detection of nephrolithiasis (radioopaque) and nephrocalcinosis
Ultrasonography and Computerized tomography scanning (CT)	Determining kidney size and shape, detecting urinary obstruction and radiolucent stones, distinguishing between simple and complex cysts, early evaluation of polycystic kidney disease, evaluation of renal mass
Intravenous pyelogram	Determining kidney size, shape, and calyceal anatomy, diagnosis of medullary sponge kidney and papillary necrosis, detection of site and cause of obstruction
Radionuclide studies	Detection of urinary obstruction and urine leak, screen for renal artery stenosis, assess renal arterial flow
Renal arteriography	Detect renal artery stenosis, assess for evidence of vasculitis, distinguish vascular vs solid mass
Voiding cystourethrogram	Detection of vesicoureteral reflux
Retrograde or antegrade pyelography	Determine site of obstruction, place ureteral stent
Magnetic resonance imaging (MRI)	Detection of renal mass, detection of renal vein thrombosis, screen for renal vascular disease using gadolinium imaging