17 - Genitourinary Disorders

Chapter 228. Approach to the Genitourinary Patient

Introduction

Although some disorders can affect both the kidneys and the lower urinary tract (eg, pyelonephritis, calculi), renal and urologic disorders usually require different approaches. Common GU symptoms include dysuria, hematospermia, hematuria, proteinuria, scrotal mass, testicular pain, and priapism. (See also Urinary Incontinence on p. 2352 and Urinary Tract Infections on p. 2373.)

Approach to the Renal Patient

In patients with renal disorders, symptoms and signs may be nonspecific, absent until the disorder is severe, or both. Findings most often are local (eg, reflecting kidney inflammation or mass), result from the systemic effects of kidney dysfunction, or affect urination (eg, changes in urine itself or in urine production).

History

History plays a limited role because symptoms are nonspecific.

Hematuria is relatively specific for a GU disorder, but patients who report red urine may instead have one of the following:

- Myoglobinuria
- Hemoglobinuria
- Porphyrinuria
- Porphobilinuria
- Food-induced urine coloring (some foods, eg, beets, rhubarb, sometimes food coloring, may make urine appear red)
- Drug-induced urine coloring (some drugs, most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methyldopa, phenacetin, phenindione, phenolphthalein, phenothiazines, and senna may make urine appear red)

High concentrations of urinary protein cause frothy or sudsy urine. Urinary frequency (see p. 2337) should be distinguished from polyuria (see p. 2324) in patients who report excessive urination. Nocturia may be a feature of either but is often the result of excess fluid intake too close to bedtime or of chronic kidney disease. Family history is useful for identifying inheritance patterns and risk of polycystic kidney disease or other hereditary nephropathies (eg, hereditary nephritis, thin basement membrane disease, nail-patella syndrome, cystinuria, hyperoxaluria).

Physical Examination

Patients with moderate or severe chronic kidney disease sometimes appear pale, wasted, or ill. Deep (Kussmaul's) respirations suggest hyperventilation in response to metabolic acidosis with acidemia.

Chest examination: Pericardial and pleuritic friction rubs may be signs of uremia.

Abdominal examination: Visual fullness of the upper abdomen is an unusual, nonspecific finding of polycystic kidney disease. It may also indicate a kidney or abdominal mass or hydronephrosis. A soft, lateralizing bruit is occasionally audible in the epigastrium or the flank in renal artery stenosis; presence of a diastolic component increases the probability of renovascular hypertension.

Pain elicited by mild striking of the back, flanks, and angle formed by the 12th rib and lumbar spine with a fist (costovertebral tenderness) may indicate pyelonephritis or urinary tract obstruction (eg, due to calculi). Normal kidneys are not usually palpable. However, in some women, the lower pole of the right kidney can occasionally be felt with palpation during deep inspiration, and large kidneys or masses can sometimes be felt without special maneuvers. In neonates, the kidneys can be felt with the thumbs when the thumbs are placed anterior and the fingers posterior to the costovertebral angle.

Transillumination can distinguish solid from cystic renal masses in some children < 1 yr if the kidney and mass are manipulated against the abdominal wall.

Skin examination: Chronic kidney disease can cause any of the following:

• Xerosis due to sebaceous and eccrine sweat gland atrophy

• Pallor due to anemia

• Hyperpigmentation due to melanin deposition

• Sallow or yellow-brown skin due to urochrome deposition

• Petechiae or ecchymoses due to platelet dysfunction

Uremic frost, the deposition of white-to-tan urea crystals on the skin after sweat evaporation, is rare.

Neurologic examination: Patients with acute renal failure may be drowsy, confused, or inattentive; speech may be slurred. Asterixis can be detected in handwriting or by observation of outstretched hands maximally extended at the wrists; after several seconds in this position, a hand flap in the flexor direction is asterixis. Asterixis suggests one of the following:

• Chronic kidney disease

• Chronic liver failure

• CO_2 narcosis

Testing

Urinalysis and measurement of serum creatinine are the initial steps in evaluation of renal disorders. Other urine, blood, and imaging tests (eg, ultrasonography, CT, MRI) are done in specific circumstances. Ideally, after the urethral meatus is cleaned, the urine specimen is collected midstream (clean-catch specimen) during the first void of the morning; the urine should be examined immediately because delays can lead to changes in test results. Bladder catheterization or suprapubic aspiration can be used for collection when urine cannot be obtained by spontaneous voiding or when vaginal material contaminates the urine specimen. However, the trauma of catheterization may falsely increase the number of RBCs in the specimen, so catheterization is usually avoided if the outcome of interest is microscopic hematuria. A specimen from a catheter collection bag is not acceptable for microscopic or bacteriologic tests.

Urinalysis: A complete urinalysis includes the following:

• Inspection for color, appearance, and odor

• Measurement of pH, specific gravity, protein, glucose, RBCs, nitrites, and WBC esterase by dipstick reagents

• Microscopic analysis for casts, crystals, and cells (urine sediment)

Bilirubin and urobilinogen, although standard parts of many dipstick tests, no longer play significant roles

in evaluation of renal or hepatic disorders.

Color is the most obvious of urine attributes, and observation of color is an integral part of urinalysis (see Table 228-1). Urine color may suggest possible causes and help direct additional testing.

Odor, often unintentionally noted during visual inspection, conveys useful information only in rare cases of inherited disorders of amino acid metabolism when urine has a distinctive smell (eg, maple syrup in maple syrup urine disease, sweaty feet in isovaleric acidemia, tomcat urine in multiple carboxylase deficiency).

[**Table 228-1.** Causes of Urine Color Changes]

pH is normally 5.0 to 6.0 (range 4.5 to 8.0). Measuring with a glass pH electrode is recommended when precise values are necessary for decision making, as when diagnosing renal tubular acidosis; in these cases, a layer of mineral oil should be added to the urine specimen to prevent escape of CO_2. Delay in processing a specimen may elevate pH because ammonia is released as bacteria break down urea. Infection with urease-producing pathogens can spuriously increase pH.

Specific gravity provides a rough measure of urine concentration (osmolality). Normal range is 1.001 to 1.035; values may be low in the elderly or in patients with impaired renal function, who are less able to concentrate urine. It is measured by hydrometer or refractometer or estimated with a dipstick. Accuracy of the dipstick test is controversial, but the test may be sufficient for patients who have calculi and are advised to self-monitor urine concentration to maintain dilute urine. Specific gravity by dipstick may be spuriously elevated when urine pH is < 6 or low when pH is > 7. Hydrometer and refractometer measurements may be elevated by high levels of large molecules (eg, radiopaque contrast agent, albumin, glucose, carbenicillin) in the urine.

Protein, detected by standard dipstick tests, reflects mainly urinary albumin concentration, classified as negative (< 10 mg/dL), trace (15 to 30 mg/dL), or 1+ (30 to 100 mg/dL) through 4+ (> 500 mg/dL). Microalbuminuria, an important marker for renal complications in patients with diabetes, is not detected by standard dipsticks, but special microalbumin dipsticks are available. Light-chain proteins (eg, due to multiple myeloma) also are not detected. Significance of proteinuria depends on total protein excretion rather than protein concentration estimated by dipstick; thus, when proteinuria is detected with dipstick testing, quantitative measures of urinary protein (see p. 2330) should be done. False-negative results can be caused by dilute urine. False-positive results can be caused by any of the following:

• High pH (> 9)

• Presence of cells

• Radiopaque contrast agents

• Concentrated urine

Glucose usually appears in the urine when serum glucose increases to > 180 mg/dL (> 10.1 mmol/L) and renal function is normal. Threshold for detection by urine dipstick is 50 mg/dL (2.8 mmol/L). Any amount is abnormal. Falsely low or negative results can result from any of the following:

• Ascorbic acid

• Ketones

• Aspirin

• Levodopa

• Tetracycline

• Very high urine pH

• Dilute urine

Hematuria is detected when RBCs lyse on a dipstick test strip, releasing Hb and causing a color change. Range is from negative (0) to 4+. Trace blood (corresponding to 3 to 5 RBCs/high-power field [HPF]) is normal under some circumstances (eg, exercise) in some people. Because the test strip reagent reacts with Hb, free Hb (eg, due to intravascular hemolysis) or myoglobin (eg, due to rhabdomyolysis) causes a positive result. Hemoglobinuria and myoglobinuria can be distinguished from hematuria by the absence of RBCs on microscopic examination and by the pattern of color change on the test strip. RBCs create a dotted or speckled pattern; free Hb and myoglobin create a uniform color change. Povidone iodine causes false-positive results (uniform coloring); ascorbic acid causes false-negative results.

Nitrites are produced when bacteria reduce urinary nitrates derived from amino acid metabolism. Nitrites are not normally present and signify bacteriuria. The test is either positive or negative. False-negative results may occur with any of the following:

• Infection with certain pathogens that cannot convert nitrate to nitrite (eg, *Enterococcus faecalis*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, *Pseudomonas* sp)

• Urine that has not stayed long enough (< 4 h) in the bladder

• Low urinary excretion of nitrate

• Enzymes (of certain bacteria) that reduce nitrates to nitrogen

• High urine urobilinogen level

• Presence of ascorbic acid

• Urine pH < 6.0

Nitrites are used mainly with WBC esterase testing to monitor patients with recurrent urine infections, particularly children with vesicoureteral reflux, and sometimes to confirm the diagnosis of uncomplicated UTI in women of childbearing age.

WBC esterase is released by lysed neutrophils. Its presence in urine reflects acute inflammation, most commonly due to bacterial infection but sometimes due to interstitial nephritis, nephrolithiasis, or renal TB. Threshold for detection is about 5 WBCs/HPF, and test results range from negative to 4+. The test is not very sensitive for detection of infection. Contamination of a urine specimen with vaginal flora is the most common cause of false-positive results. False-negative results may result from any of the following:

• Very dilute urine

• Glycosuria

• Urobilinogen

• Use of phenazopyridine, nitrofurantoin, rifampin, or large amounts of vitamin C

WBC esterase is used mainly with nitrite testing to monitor patients with recurrent urine infections and sometimes to diagnose uncomplicated UTI in women of childbearing age. If both tests are negative, the likelihood of a positive urine culture is small.

Microscopic analysis: Detection of solid elements (cells, casts, crystals) requires microscopic analysis, ideally done immediately after voiding, and dipstick testing. The specimen is prepared by centrifuging 10 to 15 mL of urine at 1500 to 2500 rpm for 5 min. The supernatant is fully decanted; a small amount of urine remains with the residue at the bottom of the centrifuge tube. The residue can be mixed back into

solution by gently agitating the tube or tapping the bottom. A single drop is pipetted onto a slide and covered with a coverslip. For routine microscopic analysis, staining is optional. The specimen is examined under reduced light with the low-power objective and under full-intensity light with the high-power objective; the latter is typically used for semiquantitative estimates (eg, 10 to 15 WBCs/HPF). Polarized light is used to identify some crystals and lipids in the urine. Phase-contrast microscopy enhances identification of cells and casts.

Epithelial cells (renal tubular, transitional, squamous cells) frequently are found in urine; most common are squamous cells lining the end of the urethra and contaminants from the vagina. Only renal tubular cells are diagnostically important; however, except when found in casts, they are difficult to distinguish from transitional cells. A few renal tubular cell casts appear in normal urine, but a large number suggests tubular injury (eg, acute tubular necrosis, tubulointerstitial nephropathy, nephrotoxins, nephrotic syndrome).

RBCs < 3/HPF may be normal (< 5/HPF is sometimes normal, eg, after exercise), and any hematuria should be interpreted in clinical context (see p. 2321). On microscopic analysis, glomerular RBCs are dysmorphic, with spicules, folding, and blebs; nonglomerular RBCs retain their normal shape.

WBCs < 5/HPF may be normal; special staining can distinguish eosinophils from neutrophils (see above). Pyuria is defined as > 5 WBCs/HPF in a sample of centrifuged urine.

Lipiduria is most characteristic of the nephrotic syndrome; renal tubular cells absorb filtered lipids, which appear microscopically as oval fat bodies, and cholesterol, which produces a Maltese cross pattern under polarized light. Lipids and cholesterol can also be free floating or incorporated into casts.

Crystals in urine are common and usually clinically insignificant (see Table 228-2). Crystal formation depends on all of the following:

• Urine concentration of crystal constituents

• pH

• Absence of crystallization inhibitors

Drugs are an underrecognized cause of crystals (see Table 228-3).

Casts are made up of glycoprotein of unknown function (Tamm-Horsfall protein) secreted from the thick ascending loop of Henle. They are cylindrical and have regular margins. Their presence indicates renal origin, which may be helpful diagnostically. Types of casts differ in constituents and appearance (see Table 228-4).

Other urine tests: Other tests are useful in specific instances.

Total protein excretion can be measured in a 24-h collection or can be estimated by the

[**Table 228-2.** Types of Urinary Crystals]

[**Table 228-3.** Drugs That Cause Crystal Formation]

protein/creatinine ratio, which, in a random urine sample, correlates well with values in g/1.73 m^2 BSA from a 24-h collection (eg, 400 mg/dL protein and 100 mg/dL creatinine in a random sample equal 4 g/1.73 m^2 in a 24-h collection). The protein/creatinine ratio is less accurate when creatinine excretion is significantly increased (eg, in muscular athletes) or decreased (eg, in cachexia).

Microalbuminuria is albumin excretion persistently between 30 and 300 mg/day (20 to 200 µg/min); lesser amounts are considered within the range of normal, and amounts > 300 mg/day (> 200 µg/min) are

considered overt proteinuria. Use of the urine albumin/urine creatinine ratio is a reliable and more convenient screening test because it avoids timed urine specimens and correlates well with 24-h values. A value > 30 mg/g (> 0.03 mg/mg) suggests microalbuminuria. The reliability of the test is best when a midmorning specimen is used, vigorous exercise is avoided before the test, and unusual creatinine production (in cachectic or very muscular patients) is not present. Microalbuminuria can occur in all of the following:

• Diabetes mellitus

• Hypertension

• Renal allograft dysfunction

• Preeclampsia

• UTI

Microalbuminuria is highly predictive of subsequent nephropathy in type 1 but not type 2 diabetes. Microalbuminuria is a risk factor for cardiovascular disorders and early cardiovascular mortality independent of diabetes or hypertension.

Sulfosalicylic acid (SSA) test strips can be used to detect protein other than albumin (eg, lgs in multiple myeloma) when dipstick urine tests are negative; urine supernatant mixed with SSA becomes turbid if protein is present. The test is semiquantitative with a scale of 0 (no turbidity) to 4+ (flocculent precipitates). Readings are falsely elevated by radiopaque contrast agents.

Ketones spill into urine with ketonemia, but use of test strips to measure urinary ketones is no longer widely recommended because they measure only acetoacetic acid and acetone, not β-hydroxybutyric acid. Thus, a false-negative result is possible even without an exogenous cause (eg, vitamin C, phenazopyridine, *N*-acetylcysteine); direct measurement of serum ketones is more accurate. Ketonuria is caused by endocrine and metabolic disorders and does not reflect renal dysfunction.

Osmolality, the total number of solute particles per unit mass (mOsm/kg [mmol/kg]), can be measured directly by osmometer. Normally, osmolality is 50 to 1200 mOsm/kg. Measurement is most useful for evaluating hypernatremia, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and diabetes insipidus.

Electrolyte measurements help diagnose specific disorders. Na level can help distinguish whether volume depletion (urine Na < 10 mEq/L) or acute tubular necrosis (urine Na > 40 mEq/L) is the cause of acute renal insufficiency or failure. The fractional excretion of Na (FE_{Na}) is the percentage of filtered Na that is excreted. It is calculated as the ratio of excreted to filtered Na, which can be simplified to the following:

$$FE_{Na} = \frac{(U_{Na})(P_{Cr})}{(P_{Na})(U_{Cr})} \times 100\%$$

where U_{Na} is urine Na, P_{Na} is plasma Na, P_{Cr} is plasma creatinine, and UCr is urine creatinine.

This ratio is a more reliable measure than U_{Na} alone because U_{Na} levels between 10 and 40 mEq/L are nonspecific. FE_{Na} < 1% suggests prerenal causes, such as volume depletion; however, acute glomerulonephritis or certain types of acute tubular necrosis (eg, rhabdomyolysis, radiocontrast-induced renal failure) can result in FE_{Na} < 1%. A value > 1% suggests acute tubular necrosis or acute interstitial nephritis.

Other useful measurements include the following:

• Fractional excretion of HCO_3 in evaluation of renal tubular acidosis (see p. 2426)

• Cl levels and urine anion gap for diagnosis of metabolic alkalosis (see p. 862) and nonanion gap metabolic acidosis (see p. 860)

• K levels in determining the cause of hypokalemia or hyperkalemia

[**Table 228-4.** Urinary Casts]

• Levels of Ca, Mg, uric acid, oxalate, citrate, and cystine in evaluation of calculi

Eosinophils, cells that stain bright red or pink-white with Wright's or Hansel staining, most commonly indicate one of the following:

• Acute interstitial nephritis

• Rapidly progressive glomerulonephritis

• Acute prostatitis

• Renal atheroembolism

Cytology is used for the following:

• To screen for cancer in high-risk populations (eg, petrochemical workers)

• To evaluate painless hematuria in the absence of glomerular disease (suggested by the absence of dysmorphic RBCs, proteinuria, and renal failure)

• To check for recurrence after bladder tumor resection

Sensitivity is about 90% for carcinoma in situ; however, sensitivity is considerably lower for low-grade transitional cell carcinomas. Inflammatory or reactive hyperplastic lesions or cytotoxic drugs for carcinoma may produce false-positive results. Accuracy for detecting bladder tumors may be increased by vigorous bladder lavage with a small volume of 0.9% saline solution (50 mL pushed in and then aspirated by syringe through a catheter). Cells collected in the saline are concentrated and examined.

Gram stain and cultures with susceptibility testing are indicated when GU tract infections are suspected; a positive result must be interpreted in the clinical context (see p. 2373).

Amino acids are normally filtered and reabsorbed by the proximal tubules. They may appear in urine when a hereditary or acquired tubular transport defect (eg, Fanconi syndrome, cystinuria) is present. Measuring type and amount of amino acids may help in the diagnosis of certain types of calculi, renal tubular acidosis, and inherited disorders of metabolism.

Blood tests: Blood tests are useful in evaluation of renal disorders.

Serum creatinine values > 1.3 mg/dL (> 114 µmol/L) in men and > 1 mg/dL (> 90 µmol/L) in women are usually abnormal. Serum creatinine depends on creatinine generation as well as renal creatinine excretion. Because creatinine turnover increases with higher muscle mass, muscular people have higher serum creatinine levels and elderly and undernourished people have lower levels.

Serum creatinine may also be increased in the following conditions:

• Use of ACE inhibitors and angiotensin II receptor blockers

• Consumption of large amounts of meat

• Use of some drugs (cimetidine, trimethoprim, cefoxitin, flucytosine)

ACE inhibitors and angiotensin II receptor blockers reversibly decrease GFR and increase serum creatinine because they vasodilate efferent more than afferent glomerular arterioles, mainly in people who are dehydrated or are receiving diuretics. In general, serum creatinine alone is not a good indicator of kidney function. The Cockcroft and Gault formula and the Modification of Diet in Renal Disease formula estimate GFR based on serum creatinine and other parameters and more reliably evaluate kidney function.

BUN/creatinine ratio is used to distinguish prerenal from renal or postrenal (obstructive) azotemia; a value > 15 is considered abnormal and may occur in prerenal and postrenal azotemia. However, BUN is affected by protein intake and by several nonrenal processes (eg, trauma, infection, GI bleeding, corticosteroids) and, although suggestive, is generally inconclusive as evidence of renal dysfunction.

Cystatin C, a serine proteinase inhibitor that is produced by all nucleated cells and filtered by the kidneys, can also be used to evaluate kidney function. Its plasma concentration is independent of sex, age, and body weight. Testing is not always available, and values are not standardized across laboratories.

Serum electrolytes (eg, Na, K, HCO_3) may become abnormal and the anion gap (Na - [Cl + HCO_3]) may increase in acute kidney injury and chronic kidney disease. Serum electrolytes should be monitored periodically.

CBC may detect anemia in chronic kidney disease or, rarely, polycythemia in renal cell carcinoma or polycystic kidney disease. Anemia is often multifactorial (mainly due to erythropoietin deficiency and sometimes worsened or caused by blood loss in dialysis circuits or the GI tract); it may be microcytic or normocytic, and may be hypochromic or normochromic.

Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Renin secretion is stimulated by reduced blood volume and renal blood flow and is inhibited by Na and water retention. Plasma renin is assayed by measuring renin activity as the amount of angiotensin I generated per hour. Specimens should be drawn from well-hydrated, Na- and K-replete patients. Plasma renin, aldosterone, cortisol, and ACTH should be measured in evaluation of all of the following:

• Adrenal insufficiency

• Hyperaldosteronism

• Refractory hypertension (see Renovascular Hypertension on p. 2077)

The plasma aldosterone/renin ratio calculated from measurements obtained with the patient in an upright posture is the best screening test for hyperaldosteronism, provided that plasma renin activity is > 0.5 ng/mL/h and aldosterone is > 12 to 15 ng/dL.

Evaluating Kidney Function

Kidney function is evaluated using values calculated from formulas based on results of blood and urine tests.

GFR: Glomerular filtration rate (GFR), the volume of blood filtered through the kidney per minute, is the best overall measure of kidney function; it is expressed in mL/min. Because normal GFR increases with increasing body size, a correction factor using body surface area (BSA) typically is applied. This correction is necessary to compare a patient's GFR to normal and to define different stages of chronic kidney disease. Given the mean normal BSA of 1.73 m^2, the correction factor is 1.73/patient BSA; adjusted GFR results are then expressed as mL/min/1.73 m^2.

Normal GFR in young, healthy adults is about 120 to 130 mL/min/1.73 m^2 and declines with age to about

75 mL/min/1.73 m^2 at age 70. Chronic kidney disease is defined by a GFR < 60 mL/min/1.73 m^2 for > 3 mo. The gold standard for GFR measurement is inulin clearance. Inulin is neither absorbed nor secreted by the renal tubule and therefore it is the ideal marker for evaluation of kidney function. However, its measurement is cumbersome and therefore it is mostly used in research settings.

Creatinine clearance: Creatinine is produced at a constant rate by muscle metabolism and is freely filtered by the glomeruli and also is secreted by the renal tubules. Because creatinine is secreted, creatinine clearance (CrCl) overestimates GFR by about 10 to 20% in people with normal kidney function and by up to 50% in patients with advanced renal failure; thus, use of CrCl to estimate GFR in chronic kidney disease is discouraged.

Using a timed (usually 24-h) urine collection, CrCl can be calculated as

$$\text{CrCl} = \text{UCr} \times \frac{\text{UVol}}{\text{PCr}}$$

where UCr is urine creatinine in mg/mL, UVol is urine volume in mL/min of collection (1440 min for a full 24-h collection), and PCr is plasma creatinine in mg/mL.

Estimating creatinine clearance: Because serum creatinine by itself is inadequate for evaluation of kidney function, several formulas have been devised to estimate CrCl using serum creatinine and other factors.

The **Cockcroft and Gault** formula can be used to estimate CrCl. It uses age, lean body weight, and serum creatinine level. It is based on the premise that daily creatinine production is 28 mg/kg/day with a decrease of 0.2 mg/yr of age.

$$\text{CrCl}_{(\text{est})} = \frac{(140 - \text{age [yr]})(\text{lean body wt [kg]})}{(72)(\text{serum creatinine [mg/dL]})}$$

$$(\times\ 0.85 \text{ if female})$$

The **modification of diet in renal disease (MDRD)** study formula (current 4-factor formula) can also be used, although it requires a calculator or computer:

$$\text{CrCl(est)} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if African-American)}$$

Approach to the Urologic Patient

Urologic patients may have symptoms referable to the kidneys as well as to other parts of the GU tract.

History

Pain originating in the kidneys or ureters is usually vaguely localized to the flanks or lower back and may radiate into the ipsilateral iliac fossa, upper thigh, testis, or labium. Typically, pain caused by calculi is colicky and may be prostrating; it is more constant if caused by infection. Acute urinary retention distal to the bladder causes agonizing suprapubic pain; chronic urinary retention causes less pain and may be asymptomatic. Dysuria is a symptom of bladder or urethral irritation (see p. 2318). Prostatic pain manifests as vague discomfort or fullness in the perineal, rectal, or suprapubic regions.

Symptoms of bladder obstruction in men include urinary hesitancy, straining, decrease in force and caliber of the urinary stream, and terminal dribbling. Incontinence has various forms (see p. 2352). Enuresis after age 3 to 4 yr may be a symptom of urethral stenosis in girls, posterior urethral valves in boys, psychologic distress, or, if onset is new, infection.

Pneumaturia (air passed with urine) suggests a vesicovaginal, vesicoenteric, or ureteroenteric fistula; the last 2 may be caused by diverticulitis, Crohn's disease, abscess, or colon cancer. Pneumaturia could also be due to emphysematous pyelonephritis.

Physical Examination

Physical examination focuses on the costovertebral angle, abdomen, rectum, groin, and genitals. Pelvic examination is usually done in women with urinary symptoms.

Costovertebral angle: Pain elicited by blunt striking of the back, flanks, and angle formed by the 12th rib and lumbar spine with a fist (costovertebral tenderness) may indicate pyelonephritis, calculi, or urinary tract obstruction.

Abdomen: Visual fullness of the upper abdomen is an extremely rare and nonspecific finding of hydronephrosis or a kidney or abdominal mass. Dullness to percussion in the lower abdomen suggests bladder distention; normally, even a full bladder cannot be percussed above the symphysis pubis. Bladder palpation can be used to confirm distention and urinary retention.

Rectum: During digital rectal examination, prostatitis may be detected as a boggy, tender prostate. Focal nodules and less discrete hard areas must be distinguished from prostate cancer. The prostate may be symmetrically enlarged, rubbery, and nontender with benign prostatic hyperplasia.

Groin and genitals: Inguinal and genital examination should be done with patients standing. Inguinal hernia or adenopathy may explain scrotal or groin pain. Gross asymmetry, swelling, erythema, or discoloration of the testes may indicate infection, torsion, tumor, or other mass. Horizontal testicular lie (bell-clapper deformity) indicates increased risk of testicular torsion. Elevation of one testis (normally the left is lower) may be a sign of testicular torsion. The penis is examined with and without retracting the foreskin. Inspection of the penis can detect

• Hypospadias or epispadias in young boys

• Peyronie's disease in men

• Priapism, ulcers, and discharge in either group

Palpation may reveal an inguinal hernia. Cremasteric reflex may be absent with testicular torsion. Location of masses in relation to the testis and the degree and location of tenderness may help differentiate among testicular masses (eg, spermatoceles, epididymitis, hydroceles, tumors). If swelling is present, the area should be transilluminated to help determine whether the swelling is cystic or solid. Fibrous plaques on the penile shaft are signs of Peyronie's disease.

Testing

Urinalysis (see p. 2307) is critical for evaluating urologic disorders. Imaging tests (eg, ultrasonography, CT, MRI) are frequently required. For semen testing, see p. 2592.

Bladder tumor antigen testing for transitional cell cancer of the urinary tract is more sensitive than urinary cytology for detecting low-grade cancer; it is not sensitive enough to replace endoscopic examination. Urine cytology is the best test to detect high-grade cancer.

Prostate-specific antigen (PSA) is a glycoprotein with unknown function produced by prostatic epithelial cells. Levels can be elevated in prostate cancer and in some common noncancerous disorders (eg, benign prostatic hyperplasia, infection, trauma). PSA is measured to detect recurrence of cancer after treatment; its widespread use for cancer screening is controversial (see p. 2470).

Imaging Tests

Imaging tests are often used to evaluate patients with renal and urologic disorders.

Plain X-Rays Without Contrast

Abdominal x-rays without radiopaque contrast agents are virtually useless in evaluation of renal and urologic disorders. These x-rays are not sensitive, showing only about 50 to 60% of renal calculi (Ca oxalate calculi and rarely staghorn calculi); calcifications consistent with calculi are also nonspecific.

X-Rays With Use of Contrast

Images taken after administration of water-soluble contrast agents highlight the kidneys and urinary collecting system. Nonionic isoosmolal agents (eg, iohexol, iopamidol) are now widely used; they have fewer adverse effects than older hyperosmolal agents but still pose a risk of acute renal injury (contrast nephropathy—see p. 3404).

In urography, an x-ray is taken after IV, percutaneous antegrade or retrograde, or cystoscopic retrograde administration of a radiopaque contrast agent. Primary contraindications for all patients are iodine allergy and risk factors for contrast nephropathy.

IVU (IV urography or pyelography): IVU has been largely superseded by rapid multidimensional CT and MRI with or without a contrast agent. When IVU is done, abdominal compression may improve visualization of the renal pelvis and proximal ureters (with application) and distal ureters (after release). Additional x-rays at 12 and 24 h after contrast administration may be indicated for detection of postrenal obstruction or hydronephrosis.

Percutaneous anterograde urography: For percutaneous anterograde urography, a radiopaque contrast agent is introduced through an existing nephrostomy tube or, less commonly, through percutaneous puncture of the renal pelvis guided by fluoroscopy. Occasionally, a ureterostomy or an ileal conduit can be used. Anterograde urography is used in the following circumstances:

- When retrograde urography is unsuccessful (eg, because of tumor obstruction at bladder level)
- When large kidney calculi requiring percutaneous surgery must be evaluated
- When transitional cell carcinoma of the upper collecting system is suspected
- When patients cannot tolerate general anesthesia or the degree of sedation required for retrograde urography

Complications relate to puncture and placement of the catheter in the GU tract and include bleeding, sepsis, injury to adjacent organs, microscopic hematuria, pain, and urinary extravasation.

Retrograde urography: Retrograde urography uses cystoscopy and ureteral catheterization to introduce a radiopaque contrast agent directly into the ureters and renal collecting system. Sedation or general anesthesia is required. This technique is used when CT or MRI is required (eg, to identify the exact location or cause of obstruction) but is unsuccessful.

It is also useful for detailed examination of the pelvicaliceal collecting system, ureters (eg, to check for ureterovaginal fistulas), and bladder. However, overdistention and back-flow may distort calyces and obscure details. Risk of infection is higher than that with other types of urography. Acute ureteral edema and secondary stricture formation are rare complications.

Cystourethrography: For cystourethrography, the radiopaque contrast agent is introduced directly into the urethra and bladder. This technique provides more details than other imaging studies for evaluation of the following:

- Vesicoureteral reflux
- Urinary incontinence

• Recurrent UTIs

• Urethral strictures

• Suspected urethral or bladder trauma

Voiding cystourethrograms are taken during urination and are used to identify posterior urethral valves. No patient preparation is necessary. Adverse effects include UTIs and urosepsis. Severe urethral stricture is a relative contraindication.

Angiography: Conventional catheter angiography has been largely replaced by noninvasive vascular imaging (eg, magnetic resonance angiography, CT angiography, ultrasonography, radionuclide scanning). Remaining indications include renal vein renin imaging, and, among patients with renal artery stenosis, angioplasty and stenting. Arteriography is also rarely used for evaluation and treatment of renal hemorrhage and before kidney-sparing surgery. Digital subtraction angiography is no longer used when rapid-sequence multidimensional CT or helical (spiral) CT is available.

Ultrasonography

Doppler ultrasonography is widely used to image the renal arteries, kidneys, bladder, prostate, testes, and penis. The test is safe but provides no information about renal function, and renal images may be difficult to obtain in overweight or obese patients. Also, there is no means to improve distinction between types of tissues, and image quality is operator-dependent. No patient preparation is necessary, but a full bladder facilitates its imaging. Ultrasonography can show urine volume after micturition (postvoiding residual). Doppler ultrasonography in patients with testicular pain helps distinguish torsion from other causes by assessing testicular blood flow.

Computed Tomography

CT provides a broad view of the urinary tract and surrounding structures. Conventional or helical scanners are used for most purposes with or without IV contrast agents. Use of contrast agents with either technique resembles IVU but provides additional detail. Helical CT without contrast agents is the study of choice for imaging of calculi. Radiopaque contrast agents are also best avoided for CT evaluation of trauma and other disorders that may involve acute hemorrhage (which appears bright white and can be confused with contrast agents) or urine extravasation. CT angiography is a less invasive alternative to conventional angiography (see p. 3405).

Magnetic Resonance Imaging

MRI is safer than CT for patients at risk of contrast nephropathy and exposes patients to no ionizing radiation. Uses include all of the following:

• Differentiation between hemorrhage and infection within renal cysts

• Determination of extent of tumor invasion within the bladder wall

• Precise imaging of the pelvis and genitals using a pelvic or endorectal coil

Magnetic resonance angiography, used to enhance images of blood vessels, has virtually replaced conventional angiography for evaluating renal artery stenosis and renal vein thrombosis in patients with normal renal function. However, nephrogenic systemic fibrosis is a risk from gadolinium-containing contrast agents, particularly when GFR is < 30 mL/min/1.73 m^2 BSA. MRI defines intrarenal calcifications poorly because they have few mobile protons. MRI with IV lymphotropic superparamagnetic nanoparticles (eg, monocrystalline iron oxide) can identify lymph node metastases in prostate cancer but is not widely available.

Radionuclide Scanning

Cortical tracers that bind to proximal tubular cells (eg, technetium-99m dimercaptosuccinic acid [^{99m}Tc DMSA]) are used to image the renal parenchyma. Excretory tracers that are rapidly filtered and excreted into urine (eg, iodine-125 iothalmate, ^{99m}Tc diethylenetriamine pentaacetic acid [DTPA], ^{99m}Tc mercaptoacetyltriglycine-3 [MAG3]) are used to assess GFR and overall renal perfusion. Radionuclide scanning can be used to evaluate renal function when use of IV contrast is undesirable. Radionuclide scanning also provides more information than does IVU or cross-sectional imaging about the following:

• Segmental renal emboli

• Renal parenchymal scarring due to vesicoureteral reflux

• Functional significance of renal artery stenosis

• Kidney function in living donors before transplantation

^{99m}Tc pertechnetate can be used to image blood flow to the testes and to distinguish torsion from epididymitis in patients with acute testicular pain, although Doppler ultrasonography is used more commonly because it is quicker. No patient preparation is necessary for radionuclide scanning, but patients should be asked about known allergies to the tracer.

Procedures

Some procedures are used for diagnosis alone, and others can be used for either diagnosis or therapy.

Bladder Catheterization

Bladder catheterization is used to do the following:

• Obtain urine for examination

• Measure residual urine volume

• Relieve urinary retention or incontinence

• Deliver radiopaque contrast agents or drugs directly to the bladder

• Irrigate the bladder

Catheterization may be urethral or suprapubic.

Catheters: Catheters vary by caliber, tip configuration, number of ports, balloon size, type of material, and length:

Caliber is standardized in French (F) units—also known as Charriere (Ch) units. Each unit is 0.33 mm, so a 14-F catheter is 4.6 mm in diameter. Sizes range from 14 to 24 F for adults and 8 to 12 F for children. Smaller catheters are usually sufficient for uncomplicated urinary drainage and useful for urethral strictures and bladder neck obstruction; bigger catheters are indicated for bladder irrigation and some cases of hemorrhage (eg, postoperatively or in hemorrhagic cystitis) and pyuria, because clots could obstruct smaller caliber catheters.

Tips are straight in most catheters (eg, Robinson, whistle-tip) and are used for intermittent urethral catheterization (ie, catheter is removed immediately after bladder drainage). Foley catheters have a straight tip and an inflatable balloon for self-retention. Other self-retaining catheters may have an expanded tip shaped like a mushroom (de Pezzer catheter) or a 4-winged perforated mushroom (Malecot catheter); they are used in suprapubic catheterization or nephrostomy. Elbowed (coude) catheters, which may have balloons for self-retention, have a bent tip to ease catheterization through strictures or

obstructions (eg, prostatic obstruction).

Ports are present in all catheters used for continuous urinary drainage. Many catheters have ports for balloon inflation, irrigation, or both (eg, 3-way Foley).

Balloons on self-retaining catheters have different volumes, from 2.5 to 5 mL in balloons intended for use in children and 10 to 30 mL in balloons used in adults. Larger balloons and catheters are generally used to manage bleeding; traction on the catheter pulls the balloon against the base of the bladder and puts pressure on vessels.

Stylets are flexible metal guides inserted through the catheter to give stiffness and to facilitate insertion through strictures or obstructions.

Catheter material chosen depends on the intended use. Plastic, latex, or polyvinyl chloride catheters are for intermittent use. Latex with silicone, hydrogel, or polymer (to diminish bacterial colonization) catheters are for continuous use. Silicone catheters are used in patients with latex allergy.

Urethral catheterization: A urethral catheter can be inserted by any health care practitioner and sometimes by patients themselves. No prior patient preparation is necessary; thus, the bladder is catheterized through the urethra unless the urethral route is contraindicated. Relative contraindications are the following:

• Urethral strictures

• Current UTI

• Urethral reconstruction or bladder surgery

• Urethral trauma

After the urethral meatus is carefully cleaned with an antibacterial solution, using strict sterile technique, the catheter is lubricated with sterile gel and gently advanced through the urethra into the bladder. Lidocaine jelly may be injected through the male urethra before the catheter is passed to help relieve discomfort.

Complications of bladder catheterization include all of the following:

• Urethral or bladder trauma with bleeding or microscopic hematuria (common)

• UTI (common)

• Creation of false passages

• Scarring and strictures

• Bladder perforation (rare)

Suprapubic catheterization: Suprapubic catheterization via percutaneous cystostomy is done by a urologist or another experienced physician. No prior patient preparation is necessary. General indications include need for long-term bladder drainage and inability to pass a catheter through the urethra or contraindication to catheter use when bladder catheterization is necessary.

Contraindications include the following:

• Inability to define bladder location clinically or ultrasonographically

• An empty bladder

• Suspected pelvic or lower abdominal adhesions

After the abdomen above the pubic area is numbed with a local anesthetic, a spinal needle is inserted into the bladder; ultrasound guidance is used if available. A catheter is then placed through a special trocar or over a guide wire threaded through the spinal needle. Prior lower abdominal surgery contraindicates blind insertion. Complications include UTI, intestinal injury, and bleeding.

Cystoscopy

Cystoscopy is insertion of a rigid or flexible fiberoptic instrument into the bladder.

Indications include the following:

• Helping diagnose urologic disorders (eg, bladder tumors or calculi)

• Treating urethral strictures

• Accessing the bladder for ureteral x-rays or placement of JJ stents (stents with coiled ends placed in the renal pelvis and bladder)

The main contraindication is active UTI.

Cystoscopy is usually done in an outpatient setting with use of local anesthesia or, when necessary, conscious sedation or general anesthesia. Complications include UTI, bleeding, and bladder and urethral trauma.

Biopsy

Biopsy requires a trained specialist (nephrologist, urologist, or interventional radiologist).

Renal biopsy: Indications for diagnostic biopsy include unexplained nephritic or nephrotic syndrome or acute kidney injury. Biopsy is occasionally done to assess response to treatment. Relative contraindications include bleeding diathesis and uncontrolled hypertension. Mild preoperative sedation with a benzodiazepine may be needed. Complications are rare but may include renal bleeding requiring transfusion or radiologic or surgical intervention.

Bladder biopsy: Bladder biopsy is indicated to diagnose certain disorders (eg, bladder cancer, sometimes interstitial cystitis or schistosomiasis) and occasionally to assess response to treatment. Contraindications include bleeding diathesis and acute tuberculous cystitis. Preoperative antibiotics are necessary only if active UTI is present. The biopsy instrument is inserted into the bladder through a cystoscope; rigid or flexible instruments can be used. The biopsy site is cauterized to prevent bleeding. A drainage catheter is left in place to facilitate healing and drainage of clots. Complications include excessive bleeding, UTI, and bladder perforation.

Prostate biopsy: Prostate biopsy is usually done to diagnose prostate cancer. Contra-indications include bleeding diathesis, acute prostatitis, and UTIs. Patient preparation includes stopping maintenance aspirin a week before biopsy, preoperative antibiotics (usually a fluoroquinolone), and an enema to clear the rectum. With the patient in a lateral position, the prostate is located by palpation or, preferably, ultrasonography. Overlying structures (perineum or rectum) are anesthetized, a spring-loaded biopsy needle is inserted into the prostate, and usually 12 tissue cores are obtained. Complications include the following:

• Urosepsis

• Hemorrhage

• Urinary retention

• Hematuria

• Hematospermia (often for 3 to 6 mo after biopsy)

Urethral Dilation

Urethral dilation is used to treat the following:

• Urethral strictures

• Urethral (urgency-frequency) syndrome

• Meatal stenosis

Contraindications include untreated infection, bleeding diathesis, a long segment stenosis, and severe scarring of the urethra. In cases of stricture, a fine filiform probe is passed through, then followers (dilators) of progressively larger diameter are attached to the distal end of the filiform probe and passed behind the probe to dilate the stricture until urine stream becomes adequate; the procedure is usually done over several sessions.

Dysuria

Dysuria is painful or uncomfortable urination, typically a sharp, burning sensation. Some disorders cause a painful ache over the bladder or perineum. Dysuria is an extremely common symptom in women, but it can affect men and can occur at any age.

Pathophysiology

Dysuria results from irritation of the bladder trigone or urethra. Inflammation or stricture of the urethra causes difficulty in starting urination and burning on urination. Irritation of the trigone causes bladder contraction, leading to frequent and painful urination. Dysuria most frequently results from an infection in the lower urinary tract, but it could also be associated with an upper UTI. Impaired renal concentrating ability is the main reason for frequent urination in upper UTIs.

Etiology

Dysuria is typically caused by urethral or bladder inflammation, although perineal lesions in women (eg, from vulvovaginitis or herpes simplex virus infection) can be painful when exposed to urine. Most cases are caused by infection, but sometimes noninfectious inflammatory disorders are responsible (see Table 228-5).

Overall, the **most common causes** of dysuria are

• Cystitis

• Urethritis from a sexually transmitted disease (STD)

Evaluation

History: History of present illness should cover duration of symptoms and whether they have occurred in the past. Important accompanying symptoms include fever, flank pain, urethral or vaginal discharge, and symptoms of bladder irritation (frequency, urgency) or obstruction (hesitancy, dribbling). Patients should be asked whether the urine is bloody, cloudy, or malodorous and the nature of any discharge (eg, thin and watery or thick and purulent). Clinicians should also ask whether patients have recently engaged in unprotected intercourse, have applied potential irritants to the perineum, have had recent urinary instrumentation (eg, cystoscopy, catheterization, surgery), or might be pregnant.

Review of systems should seek symptoms of a possible cause, including back or joint pain and eye

irritation (connective tissue disorder) and GI symptoms, such as diarrhea (reactive arthritis).

Past medical history should note prior urinary infections (including those during childhood) and any known abnormality of the urinary tract. As with any potentially infectious illness, a history of immune compromise or recent hospitalization is important.

Physical examination: Examination begins with review of vital signs, particularly to note the presence of fever.

Skin, mucosa, and joints are examined for lesions suggesting reactive arthritis (eg, conjunctivitis, oral ulcers, vesicular or crusting lesions of palms, soles, and around nails, joint tenderness). The flank is percussed for tenderness over the kidneys. The abdomen is palpated for tenderness over the bladder.

Women should have a pelvic examination to detect perineal inflammation or lesions and vaginal or cervical discharge. Swabs for STD testing and wet mount should be obtained at this time rather than doing a 2nd examination.

Men should undergo external inspection to detect penile lesions and discharge; the area under the foreskin should be examined. Testes and epididymis are palpated to detect tenderness or swelling. Rectal examination is done to palpate the prostate for size, consistency, and tenderness.

Red flags: The following findings are of particular concern:

• Fever

• Flank pain or tenderness

• Recent instrumentation

• Immunocompromised patient

• Recurrent episodes (including frequent childhood infections)

• Known urinary tract abnormality

Interpretation of findings: Some findings are highly suggestive (see Table 228-5). In young, healthy women with dysuria and significant symptoms of bladder irritation, cystitis is the most likely cause. Visible urethral or cervical discharge suggests an STD. Thick purulent material is usually gonococcal; thin or watery discharge is nongonococcal. Vaginitis and the ulcerative lesions of herpes simplex virus infection are typically apparent on inspection. In men, a very tender prostate suggests

[**Table 228-5.** Some Causes of Dysuria]

prostatitis, and a tender, swollen epididymis suggests epididymitis. Other findings also are helpful but may not be diagnostic; eg, women with findings of vulvovaginitis may also have a UTI or another cause of dysuria.

Findings suggestive of infection are more concerning in patients with red flag findings. Fever, flank pain, or both suggest an accompanying pyelonephritis. History of frequent UTIs should raise concern for an underlying anatomic abnormality or compromised immune status. Infections following hospitalization or instrumentation may indicate an atypical or resistant pathogen.

Testing: No single approach is uniformly accepted. Many clinicians presumptively give antibiotics for cystitis without any testing (sometimes not even urinalysis) in young, otherwise healthy women presenting with classic dysuria, frequency, and urgency and without red flag findings. Others evaluate everyone with a clean-catch midstream urine sample for urinalysis and culture. Some clinicians defer culture unless dipstick testing detects WBCs. In women of childbearing age, a pregnancy test is done (UTI during pregnancy is of concern because it may increase the risk of preterm labor or premature rupture of the

membranes). Vaginal discharge warrants a wet mount. Many clinicians routinely obtain samples of cervical (women) or urethral (men) exudate for STD testing (gonococcus and chlamydia culture or PCR) because many infected patients do not have a typical presentation.

A finding of > 10^5 bacteria colony-forming (CFU) units/mL suggests infection. In symptomatic patients, sometimes counts as low as 10^2 or 10^3 CFUs indicate UTI. WBCs detected with urinalysis in patients with sterile cultures are nonspecific and may occur with an STD, vulvovaginitis, prostatitis, TB, tumor, or other causes. RBCs detected with urinalysis in patients with no WBCs and sterile cultures may be due to cancer, calculus, foreign body, glomerular abnormalities, or recent instrumentation of the urinary tract.

Cystoscopy and imaging of the urinary tract may be indicated to check for obstruction, anatomic abnormalities, cancer, or other problems in patients who have no response to antibiotics, recurrent symptoms, or hematuria without infection. Pregnant patients, older patients, and patients with prolonged or recurrent dysuria need closer attention and a more thorough investigation.

Treatment

Treatment is directed at the cause. Many clinicians do not treat dysuria in women without red flag findings if no cause is apparent from examination and the results of a urinalysis. If treatment is decided upon, a 3-day course of trimethoprim/sulfamethoxazole, trimethoprim alone, or a fluoroquinolone is recommended. Some clinicians give presumptive treatment for an STD in men with similarly unremarkable findings; other clinicians await STD test results, particularly in reliable patients.

Acute, intolerable dysuria due to cystitis can be relieved somewhat by phenazopyridine 100 to 200 mg po tid for the first 24 to 48 h. This drug turns urine red-orange; patients should be cautioned not to confuse this effect with progression of infection or hematuria. Upper UTI requires 10 to 14 days of treatment with an antibiotic that is effective against gram-negative organisms, particularly *Escherichia coli*.

Key Points

• Dysuria is not always caused by a bladder infection.

• STDs should be considered.

Hematospermia

Hematospermia is blood in semen. It is often frightening to patients but is usually benign.

Pathophysiology

Semen is composed of sperm from the distal epididymis and fluids from the seminal vesicles, prostate, and Cowper's and bulbourethral glands. Thus, a lesion anywhere along this pathway could introduce blood into the semen.

Etiology

Most cases of hematospermia are

• Idiopathic

Such cases resolve spontaneously within a few days to a few months.

The most common known cause is

• Prostate biopsy

Less common causes include benign prostatic hyperplasia, infections (eg, prostatitis, urethritis,

epididymitis), and prostate cancer (in men > 35 to 40 yr). Occasionally, tumors of the seminal vesicles and testes are associated with hematospermia. Hemangiomas of the prostatic urethra or spermatic duct may cause massive hematospermia.

Schistosoma haematobium, a parasitic fluke that causes significant disease in Africa (and to a lesser extent India and parts of the Middle East), can invade the urinary tract, causing hematuria and not infrequently hematospermia. Schistosomiasis is a consideration only in men who have spent time in areas where the disorder is endemic.

Evaluation

History: History of present illness should note the duration of symptoms. Patients who do not volunteer information should be asked specifically about a recent prostate biopsy. Important associated symptoms include hematuria, difficulty starting or stopping urine flow, nocturia, burning with urination, and penile discharge.

Review of systems should note symptoms of excessive bleeding, including easy bruising, frequent nosebleeds, and excessive gum bleeding with tooth brushing or dental procedures.

Past medical history should specifically ask about known disorders of the prostate, history of or exposure to TB or HIV, risk factors for sexually transmitted diseases (STDs—eg, unprotected intercourse, multiple sex partners), known bleeding disorders, and known disorders that predispose to bleeding (eg, cirrhosis). Drug history should note use of anticoagulants or antiplatelet drugs. Patients should be asked about any family history of prostate cancer and travel to regions where schistosomiasis is endemic.

Physical examination: The external genitals should be inspected and palpated for signs of inflammation (erythema, mass, tenderness), particularly along the course of the epididymis. A digital rectal examination is done to examine the prostate for enlargement, tenderness, or a lump.

Red flags: The following findings are of particular concern:

• Symptoms lasting > 1 mo

• Palpable lesion along the epididymis or in the prostate

• Travel to a region where schistosomiasis is prevalent

Interpretation of findings: Patients whose symptoms followed prostate biopsy can be reassured that the hematospermia is harmless and will go away.

Healthy patients with a brief duration of hematospermia, an otherwise normal history and examination, and no travel history likely have an idiopathic disorder.

Patients with abnormal findings on prostate examination may have prostate cancer, benign prostatic hyperplasia, or prostatitis. Urethral discharge suggests an STD.

Epididymal tenderness suggests an STD or rarely TB (more likely in patients with risk factors of exposure or who are immunocompromised).

Characteristic findings of a bleeding disorder or use of drugs that increase risk of bleeding suggests a precipitating cause but does not rule out an underlying disorder.

Testing: In most cases, especially in men < 35 to 40 yr, hematospermia is almost always benign. If no significant abnormality is found on physical examination (including digital rectal examination), urinalysis and urine culture are done, but no further work-up is necessary.

Patients who may have a more serious underlying disorder and should have testing include those who have

• A longer duration of symptoms (> 1 mo)

• Hematuria

• Obstructive urinary symptoms

• Abnormal examination findings

These findings are of particular concern in men > 40 yr. Testing includes urinalysis, urine culture, prostate-specific antigen (PSA) testing, and transrectal ultrasonography (TRUS). Occasionally, MRI and cystoscopy are needed. Semen inspection and analysis are rarely done but can be useful when travel history suggests possible exposure to *S. haematobium*.

Treatment

Treatment is directed at the cause if known. For almost all men, reassurance that hematospermia is not a sign of cancer and does not affect sexual function is the only intervention necessary. If prostatitis is suspected, it can be treated with trimethoprim/sulfamethoxazole or a fluoroquinolone for 4 to 6 wk.

Key Points

• Most cases are idiopathic or follow prostate biopsy.

• Testing is required mainly for patients with prolonged symptoms or abnormal examination findings.

• Schistosomiasis should be considered in patients who have traveled to endemic areas.

Isolated Hematuria

Hematuria is RBCs in urine, specifically > 3 RBCs per high-power field on urine sediment examination. Urine may be red or bloody (gross hematuria) or not visibly discolored (microscopic hematuria). Isolated hematuria is urinary RBCs without other urine abnormalities (eg, proteinuria, casts).

Red urine is not always due to RBCs. Red or reddish brown discoloration may result from the following:

• Hb or myoglobin in urine

• Porphyria (most types)

• Foods (eg, beets, rhubarb, sometimes food coloring)

• Drugs (most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methyldopa, phenacetin, phenindione, phenolphthalein, phenothiazine, and senna)

Pathophysiology

RBCs may enter urine from anywhere along the urinary tract—from the kidneys, collecting system and ureters, prostate, bladder, and urethra.

Etiology

Most cases involve transient microscopic hematuria that is self-limited and idiopathic. Transient microscopic hematuria is particularly common in children, present in up to 5% of their urine samples. There are numerous specific causes (see Table 228-6).

The **most common specific causes** differ somewhat by age, but overall the most common are

• UTI

• Prostatitis

• Urinary calculi (in adults)

Cancer and prostate disease are a concern mainly in patients > 50, although younger patients with risk factors may develop cancer.

Glomerular disorders can be a cause at all ages. Glomerular disorders may represent a primary renal disorder (acquired or hereditary) or be secondary to many causes, including infections (eg, group A β-hemolytic streptococcal infection), connective tissue disorders (eg, SLE at all ages, Henoch-Schonlein purpura [HSP] in children), and blood disorders (eg, mixed cryoglobulinemia, serum sickness). Worldwide, IgA nephropathy is the most common form of glomerulonephritis.

Schistosoma haematobium, a parasitic fluke that causes significant disease in Africa (and, to a lesser extent, in India and parts of the Middle East), can invade the urinary tract, causing hematuria. Schistosomiasis is considered only if people have spent time in endemic areas.

Evaluation

History: History of present illness includes duration of hematuria and any previous episodes. Urinary obstructive symptoms (eg, incomplete emptying, nocturia, difficulty starting or stopping) and irritative symptoms (eg, irritation, urgency, frequency, dysuria) should be noted. Patients should be asked about the presence of pain and its location and severity.

Review of systems should seek symptoms of possible causes, including joint pain and rashes (connective tissue disorder).

Past medical history should include questions about any recent infections, particularly a sore throat that may indicate a group A β-hemolytic streptococcal infection. Conditions known to cause urinary tract bleeding (particularly kidney calculi, sickle cell disease or trait, and glomerular disorders) should be sought. Also, conditions that predispose to a glomerular disorder, such as a connective tissue disorder (particularly SLE and RA), endocarditis, shunt infections, and abdominal abscesses, should be identified. Risk factors for GU cancer should be identified, including smoking (the most significant), drugs (eg, cyclophosphamide, phenacetin), and exposure to industrial chemicals (eg, nitrates, nitrilotriacetate, nitrites, trichloroethylene).

Family history should identify relatives with known polycystic kidney disease, a glomerular disorder, or GU cancer. Patients should be asked about travel to areas where schistosomiasis is endemic. Drug history should note use of anticoagulants or antiplatelet drugs (although anticoagulation itself does not cause hematuria).

Physical examination: Vital signs should be reviewed for fever and hypertension.

The heart should be auscultated for murmurs (suggesting endocarditis).

The abdomen should be palpated for masses; flanks should be percussed for tenderness over the kidneys. In men, a digital rectal examination should be done to check for prostate enlargement, nodules, and tenderness.

The face and extremities should be inspected for edema (suggesting a glomerular disorder), and the skin should be inspected for rashes (suggesting vasculitis, SLE, or HSP).

Red flags: The following findings are of particular concern:

• Gross hematuria

• Persistent microscopic hematuria, especially in older patients

• Age > 50

• Hypertension and edema

Interpretation of findings: Clinical manifestations of the various causes overlap significantly, so urine and often blood tests are required. Depending on results, imaging tests may then be needed. However, some clinical findings provide helpful clues (see Table 228-6).

• Blood clots in urine essentially rule out a glomerular disorder. Glomerular disorders are often accompanied by edema, hypertension, or both; symptoms may be preceded by an infection (particularly a group A β-hemolytic streptococcal infection in children).

• Calculi usually manifest with excruciating, colicky pain. Less severe, more continuous pain is more likely to result from infection, cancer, polycystic kidney disease,

[**Table 228-6.** Some Common Specific Causes of Hematuria]

glomerulonephritis, and loin pain-hematuria syndrome.

• Urinary irritative symptoms suggest bladder or prostate infection but may accompany certain cancers (mainly bladder and prostate).

• Urinary obstructive symptoms usually suggest prostate disease.

• An abdominal mass suggests polycystic kidney disease or renal cell carcinoma.

• A family history of nephritis, sickle cell disease or trait, or polycystic kidney disease suggests that as a cause.

• Travel to Africa, the Middle East, or India suggests the possibility of schistosomiasis.

On the other hand, some common findings (eg, prostate enlargement, anticoagulant use), although potential causes of hematuria, should not be assumed to be the cause without further evaluation.

Testing: Before testing proceeds, true hematuria should be distinguished from red urine by urinalysis. In women with vaginal bleeding, the specimen should be obtained by straight catheterization to avoid contamination by a nonurinary source of blood. Red urine without RBCs suggests myoglobinuria or hemoglobinuria, porphyria, or ingestion of certain drugs or foods.

Presence of casts, protein, or dysmorphic RBCs (unusually shaped, with spicules, folding, and blebs) indicates a glomerular disorder. WBCs or bacteria suggest an infectious etiology. However, because urinalysis shows predominantly RBCs in some patients with cystitis, urine culture is usually done. A positive culture result warrants treatment with antibiotics. If hematuria resolves after treatment and no other symptoms are present, no further evaluation is required for patients < 50, especially women.

If patients < 50 (including children) have only microscopic hematuria and no urine findings suggesting a glomerular disorder, no clinical manifestations suggesting a cause, and no risk factors for cancer, they can be observed, with urinalysis repeated every 6 to 12 mo. If hematuria is persistent, ultrasonography or CT with contrast is suggested.

Patients < 50 with gross hematuria require ultrasonography or CT of the abdomen and pelvis.

If urine or clinical findings suggest a glomerular disorder, renal function is evaluated by measuring BUN, serum creatinine, and electrolytes; doing a urinalysis; and periodically determining the urine protein/creatinine ratio. Further evaluation of a glomerular disorder may require serologic tests, kidney

biopsy, or both.

All patients ≥ 50 yr require cystoscopy, as do patients who are < 50 but have risk factors, such as a family history of cancer. Men ≥ 50 require testing for prostate-specific antigen; those with elevated levels require further evaluation for prostate cancer.

Treatment

Treatment is directed at the cause.

Key Points

- Red urine should be differentiated from hematuria (RBCs in urine).
- Urinalysis and urine sediment examination help differentiate glomerular from nonglomerular causes.
- Risk of serious disease increases with aging and with duration and degree of hematuria.
- Cystoscopy and imaging tests are usually needed only for patients > 50 or for younger patients with risk factors for cancer.

Polyuria

Polyuria is urine output of > 3 L/day; it must be distinguished from urinary frequency, which is the need to urinate many times during the day or night but in normal or less-than-normal volumes. Either problem can include nocturia.

Pathophysiology

Water homeostasis is controlled by a complex balance of water intake (itself a matter of complex regulation), renal perfusion, glomerular filtration and tubular reabsorption of solutes, and reabsorption of water from the renal collecting ducts.

When water intake increases, blood volume increases and thus renal perfusion and GFR increase, resulting in increased urine volume. However, the increased water intake lowers blood osmolality, decreasing release of ADH (also referred to as arginine vasopressin) from the hypothalamic-pituitary system. Because ADH promotes water reabsorption in the renal collecting ducts, decreased levels of ADH increase urine volume, allowing body water to return to normal.

Additionally, high amounts of solutes within the renal tubule cause a passive osmotic diuresis (solute diuresis) and thus an increase in urine volume. The classic example of this process is the glucose-induced osmotic diuresis in uncontrolled diabetes mellitus, when high urinary glucose levels (> 250 mg/dL) exceed tubular reabsorption capacity, leading to high glucose levels in the renal tubules; water follows passively, resulting in glucosuria and increased urine volume.

Therefore, polyuria results from any process that involves

- Sustained increase in water intake (polydipsia)
- Decreased ADH secretion (central diabetes insipidus)
- Decreased peripheral ADH sensitivity (nephrogenic diabetes insipidus)
- Solute diuresis

Etiology

The most common cause of polyuria (see

Table 228-7) in both adults and children is

• Uncontrolled diabetes mellitus

[**Table 228-7.** Some Causes of Polyuria]

In the absence of diabetes mellitus, the most common causes are

• Primary polydipsia

• Central diabetes insipidus

• Nephrogenic diabetes insipidus

Evaluation

History: History of present illness should include the amounts of fluid consumed and voided to distinguish between polyuria and urinary frequency. If polyuria is present, patients should be asked about the age at onset, rate of onset (eg, abrupt vs gradual), and any recent clinical factors that may cause polyuria (eg, IV fluids, tube feedings, resolution of urinary obstruction, stroke, head trauma, surgery).

Review of systems should seek symptoms suggesting possible causes, including dry eyes and dry mouth (Sjogren's syndrome) and weight loss and night sweats (cancer).

Past medical history should be reviewed for conditions associated with polyuria, including diabetes mellitus, psychiatric disorders, sickle cell disease, sarcoidosis, amyloidosis, and hyperparathyroidism. A family history of polyuria should be noted. Drug history should note use of any drugs associated with nephrogenic diabetes insipidus (see Table 228-7) and agents that increase urine output (eg, diuretics, alcohol, caffeinated beverages).

Physical examination: The general examination should note signs of obesity (as a risk factor for type 2 diabetes mellitus) or undernutrition or cachexia that might reflect an underlying cancer or an eating disorder with surreptitious diuretic use.

The head and neck examination should note dry eyes or dry mouth (Sjogren's syndrome). Skin examination should note the presence of any hyperpigmented or hypopigmented lesions, ulcers, or subcutaneous nodules that may suggest sarcoidosis. Comprehensive neurologic examination should note any focal deficits that suggest an underlying neurologic insult and assess mental status for indications of a thought disorder.

Red flags: The following findings are of particular concern:

• Abrupt onset or onset during the first few years of life

• Night sweats, cough, and weight loss, especially when there is an extensive smoking history

• Psychiatric disorder

Interpretation of findings: History can often distinguish polyuria from frequency, but rarely a 24-h urine collection may be needed.

Clinical evaluation may suggest a cause (see Table 228-7), but testing is usually necessary. Diabetes insipidus is suggested by a history of cancer or chronic granulomatous disease (due to hypercalcemia), use of certain drugs (lithium, cidofovir, foscarnet, ifosfamide), and less common conditions (eg, sickle cell disease, renal amyloidosis, sarcoidosis, Sjogren's syndrome) that have manifestations that are often more prominent than and precede the polyuria.

Abrupt onset of polyuria at a precise time suggests central diabetes insipidus, as does preference for

extremely cold or iced water. Onset during the first few years of life is typically related to inherited central or nephrogenic diabetes insipidus or uncontrolled type 1 diabetes mellitus. Polyuria caused by diuresis is suggested by a history of diuretic use or diabetes mellitus. Psychogenic polydipsia is more common in patients with a history of a psychiatric disorder (primarily bipolar disorder or schizophrenia) rather than as an initial manifestation.

Testing: Once excess urine output has been verified by history or measurements, serum or fingerstick glucose determination should be done to rule out uncontrolled diabetes.

If hyperglycemia is not present, then testing is required:

• Serum and urine chemistries (electrolytes, Ca)

• Serum and urine osmolality and sometimes plasma ADH level

These tests look for hypercalcemia, hypokalemia (due to surreptitious diuretic use), and hypernatremia or hyponatremia:

• Hypernatremia (Na > 142 mEq/L) suggests excess free water loss due to central or nephrogenic diabetes insipidus.

• Hyponatremia (Na < 137 mEq/L) suggests excess free water intake secondary to polydipsia.

• Urine osmolality is typically < 300 mOsm/kg with water diuresis and > 300 mOsm/kg with solute diuresis.

If the diagnosis remains unclear, then measurement of serum and urine Na and osmolality in response to a **water deprivation test** and exogenous ADH administration should be done. Because serious dehydration may result from this testing, the test should be done only while patients are under constant supervision; hospitalization is usually required. Additionally, patients in whom psychogenic polydipsia is suspected must be observed to prevent surreptitious drinking.

The test is started in the morning by weighing the patient, obtaining venous blood to determine serum electrolyte concentrations and osmolality, and measuring urine osmolality. Voided urine is collected hourly, and its osmolality is measured. Dehydration is continued until orthostatic hypotension and postural tachycardia appear, ≥ 5% of the initial body weight has been lost, or the urinary concentration does not increase > 30 mOsm/kg in sequentially voided specimens. Serum electrolytes and osmolality are again determined, and 5 units of aqueous vasopressin are injected sc. Urine for osmolality measurement is collected one final time 60 min postinjection, and the test is terminated.

A normal response produces maximum urine osmolality after dehydration (> 700 mOsm/kg), and osmolality does not increase more than an additional 5% after injection of vasopressin.

In **central diabetes insipidus,** patients are typically unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality after vasopressin administration. The increase in urine osmolality is 50 to 100% in central diabetes insipidus vs 15 to 45% with partial central diabetes insipidus.

In **nephrogenic diabetes insipidus,** patients are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration. Occasionally in partial nephrogenic diabetes insipidus, the increase in urine osmolality can be up to 45%, but overall these numbers are much lower than those that occur in partial central diabetes insipidus (usually < 300 mOsm/kg).

In **psychogenic polydipsia,** urine osmolality is < 100 mOsm/kg. Decreasing water intake will lead to decreasing urine output, increasing plasma osmolality and serum Na concentration.

Measurement of circulating ADH is the most direct method of diagnosing central diabetes insipidus. Levels at the end of the water deprivation test (before the vasopressin injection) are low in central

diabetes insipidus and appropriately elevated in nephrogenic diabetes insipidus. However, ADH levels are not routinely available. In addition, water deprivation is so accurate that direct measurement of ADH is rarely necessary. Plasma ADH levels are diagnostic after either dehydration or infusion of hypertonic saline.

Treatment

Treatment varies by cause.

Key Points

- Uncontrolled diabetes mellitus is the most common cause of polyuria in both adults and children.
- In the absence of diabetes mellitus, the most common causes of chronic polyuria are primary polydipsia, central diabetes insipidus, and nephrogenic diabetes insipidus.
- Hypernatremia usually indicates central or nephrogenic diabetes insipidus.
- Hyponatremia is more characteristic of polydipsia.
- Abrupt onset of polyuria suggests central diabetes insipidus.
- A water deprivation test can help with diagnosis but should only be done with the patient under close supervision.

Priapism

Priapism is painful, persistent, abnormal erection unaccompanied by sexual desire or excitation. It is most common in boys 5 to 10 yr and in men age 20 to 50 yr.

Pathophysiology

The penis is composed of 3 corporeal bodies: 2 corpora cavernosa and 1 corpus spongiosum. Erection is the result of smooth muscle relaxation and increased arterial flow into the corpora cavernosa, causing engorgement and rigidity.

Ischemic priapism: Most cases of priapism involve failure of detumescence and are most commonly due to failure of venous outflow (ie, low flow), also known as ischemic priapism. Severe pain from ischemia occurs after 4 h. If prolonged > 4 h, priapism can lead to corporeal fibrosis and subsequent erectile dysfunction or even penile necrosis and gangrene.

Stuttering priapism is a recurrent form of ischemic priapism with repeated episodes and intervening periods of detumescence.

Nonischemic priapism: Less commonly, priapism is due to unregulated arterial inflow (ie, high flow), usually as a result of formation of an arterial fistula after trauma. Nonischemic priapism is not painful and does not lead to necrosis. Subsequent erectile dysfunction is common.

Etiology

In adults, the most common cause (see Table 228-8) is

- Drug therapy for erectile dysfunction

In children, the most common causes are

- Hematologic disorders (eg, sickle cell disease, less commonly leukemia)

[Table 228-8. Some Causes of Priapism]

In many cases, priapism may be idiopathic and recurrent.

Evaluation

Priapism requires urgent treatment to prevent chronic complications (primarily erectile dysfunction). Evaluation and treatment should be done simultaneously.

History: History of present illness should cover the duration of erection, presence of partial or complete rigidity, presence or absence of pain, and any recent or past genital trauma. The drug history should be reviewed for offending drugs, and patients should be directly asked about the use of recreational drugs and drugs used to treat erectile dysfunction.

Review of systems should seek symptoms suggesting a cause, including dysuria (UTIs), urinary hesitancy or frequency (prostate cancer), fever and night sweats (leukemia), and lower-extremity weakness (spinal cord pathology).

Past medical history should identify known conditions associated with priapism (see Table 228-8), particularly hematologic disorders. Patients should be asked about a family history of hemoglobinopathies (sickle cell disease or thalassemia).

Physical examination: A focused genital examination should be done to evaluate extent of rigidity and tenderness and determine whether the glans and corpus spongiosum are also affected. Penile or perineal trauma and signs of infection, inflammation, or gangrenous change should be noted.

The general examination should note any psychomotor agitation, and the head and neck examination should look for pupillary dilation associated with stimulant use. The abdomen and suprapubic area should be palpated to detect any masses or splenomegaly, and a digital rectal examination should be done to detect prostatic enlargement or other pathology. Neurologic examination is useful to detect any signs of lower-extremity weakness or saddle paresthesias that might indicate spinal pathology.

Red flags: The following findings are of particular concern:

• Pain

• Priapism in a child

• Recent trauma

• Fever and night sweats

Interpretation of findings: In most cases, the clinical history reveals a history of drug treatment for erectile dysfunction, illicit drug use, or a history of sickle cell disease or trait; in these cases, no testing is indicated.

In patients with ischemic priapism, physical examination typically reveals complete rigidity with pain and tenderness of the corpus cavernosa and sparing of the glans and corpus spongiosum. By contrast, nonischemic priapism is painless and nontender, and the penis may be partially or completely rigid.

Testing: If the cause is not obvious, screening is done for hemoglobinopathies, leukemia, lymphoma, UTI, and other causes:

• CBC

• Urinalysis and culture

• Hb electrophoresis in blacks and men of Mediterranean descent

Many clinicians also do drug screening, intracavernosal ABG testing, and duplex ultrasonography. Penile duplex ultrasonography will show little or absent cavernosal blood flow in men with ischemic priapism and normal to high cavernosal blood flow in men with nonischemic priapism. Ultrasonography may also reveal anatomic abnormalities, such as cavernous arterial fistula or pseudoaneurysm, which usually indicate nonischemic priapism. Occasionally, MRI with contrast is useful to demonstrate arteriovenous fistulas or aneurysms.

Treatment

Treatment is often difficult and sometimes unsuccessful, even when the etiology is known. Whenever possible, patients should be referred to an emergency department; patients should preferably be seen and treated by a urologist. Other disorders should be treated. For example, priapism often resolves when sickle cell crisis is treated. Measures used to treat priapism itself depend on the type.

Ischemic priapism: Treatment should begin immediately, typically with aspiration of blood from the base of one of the corpora cavernosa using a nonheparinized syringe, often with saline irrigation and intracavernous injection of the α-receptor agonist phenylephrine. For phenylephrine injections, 1 mL of 1% phenylephrine (10 mg/mL) is added to 19 mL of 0.9% saline to make 500 µg/mL; 100 to 500 µg (0.2 to 1 mL) is injected every 5 to 10 min until relief occurs or a total dose of 1000 µg is given. Before aspiration or injection, anesthesia is provided with a dorsal nerve block or local infiltration.

If these measures are unsuccessful or if priapism has lasted > 48 h (and is thus unlikely to resolve with these measures), a surgical shunt can be created between the corpus cavernosum and glans penis or corpus spongiosum and another vein.

Stuttering priapism: Stuttering priapism, when acute, is treated in the same way as other forms of ischemic priapism. There is a report of several cases caused by sickle cell disease that responded to a single oral dose of sildenafil. Treatments that may help prevent recurrences of stuttering priapism include antiandrogen therapy with gonadotropin-releasing hormone analogs, estrogen, bicalutamide, flutamide, phosphodiesterase type-5 inhibitors, and ketoconazole. The goal of antiandrogen therapy is to decrease the plasma testosterone level to < 10% of normal. Digoxin, terbutaline, gabapentin, and hydroxyurea have also been tried with some success.

Nonischemic priapism: Conservative therapy (eg, ice packs and analgesics) is usually successful; if not, selective embolization or surgery is indicated.

Refractory priapism: If other treatments are ineffective, a penile prosthesis can be placed.

Key Points

• Priapism requires urgent evaluation and treatment.

• Drugs (prescription and recreational) and sickle cell disease are the most common causes.

• Acute treatment is with α-agonists, needle decompression, or both.

Proteinuria

Proteinuria is protein, usually albumin, in urine. High concentrations of protein cause frothy or sudsy urine. In many renal disorders, proteinuria occurs with other urinary abnormalities (eg, hematuria). Isolated proteinuria is urinary protein without other symptoms or urinary abnormalities.

Pathophysiology

Although the glomerular basement membrane is a very effective barrier against larger molecules (eg, most plasma proteins, including albumin), a small amount of protein passes through the capillary

basement membranes into the glomerular filtrate. Some of this filtered protein is degraded and reabsorbed by the proximal tubules, but some is excreted in the urine. The upper limit of normal urinary protein excretion is considered to be 150 mg/day, which can be measured in a 24-h urine collection or estimated by random urine protein/creatinine ratio (values < 0.3 are abnormal); for albumin it is about 30 mg/day. Albumin excretion between 30 and 300 mg/day (20 to 200 µg/min) is considered microalbuminuria, and higher levels are considered macroalbuminuria. Mechanisms of proteinuria may be categorized as

• Glomerular

• Tubular

• Overflow

• Functional

Glomerular proteinuria results from glomerular disorders, which typically involve increased glomerular permeability; this permeability allows increased amounts of plasma proteins (sometimes very large amounts) to pass into the filtrate.

Tubular proteinuria results from renal tubulointerstitial disorders that impair reabsorption of protein by the proximal tubule, causing proteinuria (mostly from smaller proteins such as immunoglobulin light chains rather than albumin). Causative disorders are often accompanied by other defects of tubular function (eg, HCO_3 wasting, glycosuria, aminoaciduria) and sometimes by glomerular pathology (which also contributes to the proteinuria).

Overflow proteinuria occurs when excessive amounts of small plasma proteins (eg, immunoglobulin light chains produced in multiple myeloma) exceed the reabsorptive capacity of the proximal tubules.

Functional proteinuria occurs when increased renal blood flow (eg, due to exercise, fever, high-output heart failure) delivers increased amounts of protein to the nephron, resulting in increased protein in the urine (usually < 1 g/day). Functional proteinuria reverses when renal blood flow returns to normal.

Orthostatic proteinuria is a benign condition (most common among children and adolescents) in which proteinuria occurs mainly when the patient is upright. Thus, urine typically contains more protein during waking hours (when people are more often upright) than during sleep. It has a very good prognosis and requires no special intervention.

Consequences: Proteinuria caused by renal disorders usually is persistent (ie, present on serial testing) and, when in the nephrotic range, can cause significant protein wasting. Presence of protein in the urine is toxic to the kidneys and causes renal damage.

Etiology

Causes can be categorized by mechanism. The most common causes of proteinuria are glomerular disorders, typically manifesting as nephrotic syndrome (see Table 228-9).

The most common causes in adults are

• Focal segmental glomerulosclerosis

• Membranous nephropathy

• Diabetic nephropathy

The most common causes in children are

• Minimal change disease (in young children)

• Focal segmental glomerulosclerosis (in older children)

Evaluation

Proteinuria itself is usually recognized only on urinalysis or urine dipstick testing. History and physical examination occasionally give clues to cause.

History and physical examination: The **review of systems** seeks symptoms suggesting cause, including red or brown urine (glomerulonephritis) or bone pain (myeloma).

Patients are asked about existing conditions that can cause proteinuria, including recent serious illness (particularly with fever), intense physical activity, known renal disorders, diabetes, pregnancy, sickle cell disease, SLE, and cancer (particularly myeloma and related disorders).

Physical examination is of limited use, but vital signs should be reviewed for increased BP, suggesting glomerulonephritis. The examination should seek signs of peripheral edema and ascites reflective of fluid overload and possibly a glomerular disorder.

Testing: Urine dipstick primarily detects albumin. Precipitation techniques, such as heating and sulfosalicylic acid test strips, detect all proteins. Thus, isolated proteinuria detected incidentally is usually albuminuria. Dipstick testing is relatively insensitive for detection of microalbuminuria, so a positive urine dipstick test usually suggests overt proteinuria. Dipstick testing is also unlikely to detect excretion of smaller proteins characteristic of tubular and overflow proteinuria.

Patients with a positive dipstick test (for protein or any other component) should have routine microscopic urinalysis. Abnormalities on urinalysis (eg, casts and dysmorphic RBCs suggesting glomerulonephritis; glucose, ketones, or both suggesting diabetes) or disorders suggested by history and physical examination (eg, peripheral edema suggesting a glomerular disorder) require further work up.

If urinalysis is otherwise normal, further testing can be deferred pending repeat urine protein assessment. If proteinuria is no longer present, particularly in patients who have had recent intense exercise, fever, or heart failure exacerbation, functional proteinuria is likely. Persistent proteinuria is a sign of a glomerular disorder and requires further testing and referral to a nephrologist. Further testing includes CBC; measurement of serum electrolytes, BUN, creatinine, and glucose; determination of GFR (see p. 2312); quantification of urinary protein (by 24-h measurement or random urine protein/creatinine ratio); and evaluation of kidney size (by ultrasonography or CT). In most patients with glomerulopathy, proteinuria is in the nephrotic range (> 3.5 g/day or urine protein/creatinine ratio > 2.7).

[**Table 228-9.** Causes of Proteinuria]

Other testing is usually done to determine the cause of a glomerular disorder, including lipid profile, complement levels, cryoglobulins, hepatitis B and C serology, antinuclear antibody testing, and urine and serum protein electrophoresis. If these noninvasive tests are not diagnostic (as is often the case), renal biopsy is necessary. Unexplained proteinuria and renal failure, especially in older patients, could be due to myelodysplastic disorders (eg, multiple myeloma) or amyloidosis.

Among patients < 30 yr, orthostatic proteinuria should be considered. Diagnosis requires 2 urine collections, one done from 7 AM to 11 PM (day sample) and the other from 11 PM to 7 AM (night sample). The diagnosis is confirmed if the urinary protein exceeds normal values in the day sample (or if urine protein/creatinine ratio is > 0.3) and does not in the night sample.

Treatment

Treatment is directed at the cause.

Painless Scrotal Mass

A painless scrotal mass is often noticed by the patient but may be an incidental finding on routine physical examination.

Scrotal pain and painful scrotal masses or swelling (see p. 2334) can be caused by testicular torsion, appendiceal torsion, epididymitis, epididymo-orchitis, scrotal abscess, trauma, strangulated inguinal hernias, orchitis, and Fournier's gangrene.

Etiology

There are several causes (see Table 228-10) of a painless scrotal mass but the most common include the following:

• Hydrocele

• Nonincarcerated inguinal hernia

• Varicocele (present in up to 20% of adult men)

Less common causes include spermatocele, hematocele, fluid overload, and occasionally testicular cancer. Testicular cancer is the most concerning cause of a painless scrotal mass. Although it is rare compared with the other listed causes, it is the most common solid cancer in men < 40 yr; because it responds well to treatment, prompt recognition is important.

Evaluation

History: History of present illness should address duration of symptoms, the effect of upright position and increase in intra-abdominal pressure, and presence and characteristics of associated symptoms such as pain.

Review of systems should seek symptoms suggesting possible causes, including abdominal pain, anorexia, or vomiting (inguinal hernia with intermittent strangulation); dyspnea and leg swelling (right heart failure); abdominal distention (ascites); and decreased libido, feminization, and infertility (testicular atrophy with bilateral varicoceles).

Past medical history should identify existing disorders that can cause masses (eg, right heart failure, ascites causing bilateral lymphedema); known scrotal disorders (eg, testicular tumor or epididymitis causing hydrocele); and inguinal hernia.

Physical examination: Physical examination includes evaluation for systemic disorders that can cause edema (eg, heart failure, ascites) and detailed inguinal and genital examination.

Inguinal and genital examination should be done with patients standing and recumbent. The inguinal area is inspected and palpated, particularly for reducible masses. The testes, epididymides, and spermatic cords should be palpated for swelling, masses, and tenderness. Careful palpation can usually localize a discrete mass to one of these structures. Nonreducible masses should be transilluminated to help determine whether they are cystic or solid.

Red flags: The following findings are of particular concern:

• Nonreducible mass that obscures normal spermatic cord structures

• Mass that is part of or attached to the testis and does not transilluminate

Interpretation of findings: A nonreducible mass that obscures normal spermatic cord structures suggests an incarcerated inguinal hernia. If a mass is part of or attached to the testis and does not transilluminate, testicular cancer is possible.

Other clinical characteristics can provide important clues (see Table 228-10). For example, a mass that transilluminates is probably cystic (eg, hydrocele, spermatocele). A mass that disappears or becomes smaller when recumbent suggests varicocele, inguinal hernia, or communicating hydrocele. The presence of a hydrocele makes assessment for other scrotal masses by examination difficult. Rarely, a varicocele persists when the patient is recumbent or is present on the right side; either finding suggests inferior vena caval obstruction.

Testing: Clinical evaluation may be diagnostic (eg, in varicocele, lymphedema, inguinal hernia); otherwise, testing is typically done. Ultrasonography is done when

• The diagnosis is uncertain

• Usually when hydrocele is present (to diagnose causative scrotal lesions)

• The mass does not transilluminate

If ultrasonography confirms a solid testicular mass, further testing is done for testicular cancer (see p. 2476), including the following:

• β-Human chorionic gonadotropin level (hCG)

• α-Fetoprotein level

• LDH level

• CT of the abdomen

Treatment

Treatment is directed at the cause. No treatment is indicated for all masses. If inguinal hernia is suspected, reduction can be attempted (see p. 114).

[**Table 228-10.** Some Causes of a Painless Scrotal Mass]

Key Points

• A nonreducible mass that obscures normal spermatic cord structures suggests an incarcerated inguinal hernia.

• A solid mass, one that does not transilluminate, or both mandates evaluation for testicular cancer.

• The cause of a hydrocele must be determined.

Scrotal Pain

Scrotal pain can occur in males of any age, from neonates to the elderly.

Etiology

The most common causes of scrotal pain include

• Testicular torsion

• Torsion of the testicular appendage

• Epididymitis

There are a number of less common causes (see

Table 228-11). Age, onset of symptoms, and other findings can help determine the cause.

Evaluation

Expeditious evaluation, diagnosis, and treatment are required because untreated testicular torsion may cause loss of a testis.

History: History of present illness should determine location (unilateral or bilateral), onset (acute or subacute), and duration of pain. Important associated symptoms include fever, dysuria, penile discharge, and presence of scrotal mass. Patients should be asked about preceding events, including injury, straining or lifting, and sexual contact.

Review of systems should seek symptoms of causative disorders, including purpuric rash, abdominal pain, and arthralgias (Henoch-Schonlein purpura); intermittent scrotal masses, groin swelling, or both (inguinal hernia); fever and parotid gland swelling (mumps orchitis); and flank pain or hematuria (renal calculus).

Past medical history should identify known disorders that may cause referred pain, including hernias, abdominal aortic aneurysm, renal calculi, and risk factors for serious disorders, including diabetes and peripheral vascular disease (Fournier's gangrene).

Physical examination: Physical examination begins with a review of vital signs and assessment of the severity of pain. Examination focuses on the abdomen, inguinal region, and genitals.

The abdomen is examined for tenderness and masses (including bladder distention). Flanks are percussed for costovertebral angle tenderness.

Inguinal and genital examination should be done with the patient standing. Inguinal area is inspected and palpated for adenopathy, swelling, or erythema. Examination of the penis should note ulcerations, urethral discharge, and piercings and tattoos (sources of bacterial infections). Scrotal examination should note asymmetry, swelling, erythema or discoloration, and positioning of the testes (horizontal vs vertical, high vs low). Cremasteric reflex should be tested bilaterally. The testes, epididymides, and spermatic cords should be palpated for swelling and tenderness. If swelling is present, the area should be transilluminated to help determine whether the swelling is cystic or solid.

Red flags: The following findings are of particular concern:

- Sudden onset of pain; exquisite tenderness; and a high-riding, horizontally displaced testis (testicular torsion)
- Inguinal or scrotal nonreducible mass with severe pain, vomiting, and constipation (incarcerated hernia)
- Scrotal or perineal erythema, necrotic or blistered skin lesions, and toxic appearance (Fournier's gangrene)
- Sudden onset of pain, hypotension, weak pulse, pallor, dizziness, and confusion (ruptured abdominal aortic aneurysm)

Interpretation of findings: The focus is to distinguish causes that require immediate treatment from others. Clinical findings provide important clues (see Table 228-11).

Aortic catastrophes and Fournier's gangrene occur primarily in patients > 50 yr; the other conditions that require immediate treatment can occur at any age. However, testicular torsion is most common in neonates and postpubertal boys, torsion of the testicular appendage occurs most commonly in prepubertal boys (7 to 14 yr), and epididymitis is most common in adolescents and adults.

Severe, sudden onset of pain suggests testicular torsion or renal calculus. Pain from epididymitis, incarcerated hernia, or appendicitis is of more gradual onset. Patients with torsion of the testicular

appendage present with moderate pain that develops over a few days; pain is localized to the upper pole. Bilateral pain suggests infection (eg, orchitis, particularly if accompanied by fever and viral symptoms) or a referred cause. Flank pain that radiates to the scrotum suggests renal calculus or, in men > 55 yr, abdominal aortic aneurysm.

Normal findings on scrotal and perineal examination suggest referred pain. Attention must then be directed to extrascrotal disorders, particularly appendicitis, renal calculi, and, in men > 55, abdominal aortic aneurysm.

Abnormal scrotal and perineal examination findings often suggest a cause. Sometimes, early in epididymitis, tenderness and induration may be localized to the epididymis; early in torsion, the testis may be clearly high-riding, with a horizontal lie and the epididymis not

[**Table 228-11.** Some Causes of Scrotal Pain]

particularly tender. However, frequently the testis and epididymis are both swollen and tender, there is scrotal edema, and it is not possible to differentiate epididymitis from torsion by palpation. However, the cremasteric reflex is absent in torsion, as are findings of a sexually transmitted disease (STD—eg, purulent urethral discharge); the presence of both of these findings makes epididymitis quite likely.

Sometimes, a scrotal mass caused by a hernia may be palpable in the inguinal canal; in other cases, hernia can be difficult to distinguish from testicular swelling.

Painful erythema of the scrotum with no tenderness of the testes or epididymides should raise suspicion of infection, either cellulitis or early Fournier's gangrene.

A vasculitic rash, abdominal pain, and arthralgias are consistent with a systemic vasculitis syndrome such as Henoch-Schonlein purpura or polyarteritis nodosa.

Testing: Testing is typically done.

• Urinalysis and culture (all patients)

• STD testing (all patients with positive urinalysis, discharge, or dysuria)

• Color Doppler ultrasonography to rule out torsion (no clear-cut alternate cause)

• Other testing as suggested by findings (see Table 228-11)

Urinalysis and culture are always required. Findings of UTI (eg, pyuria, bacteriuria) suggest epididymitis. Patients with findings that suggest UTI and patients with urethral discharge or dysuria should be tested for STDs as well as other bacterial causes of UTI.

Timely diagnosis of testicular torsion is critical. If findings are highly suggestive of torsion, immediate surgical exploration is done in preference to testing. If findings are equivocal and there is no clear alternate cause of acute scrotal pain, color Doppler ultrasonography is done. If Doppler ultrasonography is not available, radionuclide scanning may be used but is less sensitive and specific.

Treatment

Treatment is directed at the cause and can range from emergency surgery (testicular torsion) to bedrest (torsion of the testicular appendage). If testicular torsion is present, prompt surgery (< 12 h after presentation) is generally required. Delayed surgery may lead to testicular infarction, long-term testicular damage, or the loss of a testis. Surgical detorsion of the testis relieves the pain immediately, and simultaneous bilateral orchiopexy prevents recurrence of torsion.

Analgesics, such as morphine or other opioids, are indicated for the relief of acute pain. Antibiotics are indicated for cases of bacterial epididymitis or orchitis.

Geriatrics Essentials

Testicular torsion is uncommon in elderly men, and when present, the manifestations are usually atypical and therefore diagnosis is delayed. Epididymitis, orchitis, and trauma are more common in elderly men. Occasionally, inguinal hernia, colon perforation, or renal colic may cause scrotal pain in elderly men.

Key Points

- Always consider testicular torsion in patients with acute scrotal pain, particularly in children and adolescents; quick, accurate diagnosis is essential.
- Other common causes of scrotal pain are torsion of the testicular appendage and epididymitis.
- Color Doppler ultrasonography is usually done when the diagnosis is unclear.
- Normal findings on scrotal and perineal examination suggest referred pain.

Urinary Frequency

Urinary frequency is the need to urinate many times during the day, at night (nocturia), or both but in normal or less-than-normal volumes. Frequency may be accompanied by a sensation of an urgent need to void (urinary urgency). Urinary frequency is distinguished from polyuria, which is urine output of > 3 L/day.

Pathophysiology

Urinary frequency usually results from disorders of the lower GU tract. Inflammation of the bladder, urethra, or both causes a sensation of the need to urinate. However, this sensation is not relieved by emptying the bladder, so once the bladder is emptied, patients continue trying to void but pass only small volumes of urine.

Etiology

There are many causes of urinary frequency (see Table 228-12), but the most common include

- UTIs
- Urinary incontinence
- Benign prostatic hyperplasia (BPH)
- Urinary tract calculi

Evaluation

History: History of present illness should first ask about the amounts of fluid consumed and voided to distinguish between urinary frequency and polyuria. If urinary frequency is present, patients are asked about acuity of onset, presence or absence of irritative symptoms (eg, irritation, urgency, dysuria), obstructive symptoms (eg, hesitancy, poor flow, sensation of incomplete voiding, nocturia), and recent sexual contacts.

Review of systems should cover symptoms suggestive of a cause, including fever, flank or groin pain, and hematuria (infection); missed menses, breast swelling, and morning sickness (pregnancy); and arthritis and conjunctivitis (reactive arthritis).

Past medical history should ask about known causes, including prostate disease and previous pelvic

radiation or surgeries. Drugs and diet are reviewed for the use of agents that increase urine output (eg, diuretics, alcohol, caffeinated beverages).

Physical examination: Examination focuses on the GU system.

Any urethral discharge or any lesions consistent with sexually transmitted diseases are noted. Rectal examination in men should note the size and consistency of the prostate; pelvic examination in women should note the presence of any cystocele. Patients should be instructed to cough while the urethra is observed for signs of urinary leakage.

The costovertebral angle should be palpated for tenderness, and the abdominal examination should note the presence of any masses or suprapubic tenderness.

Neurologic examination should test for lower-extremity weakness.

Red flags: The following findings are of particular concern:

• Lower-extremity weakness

• Fever and back pain

Interpretation of findings: Dysuria suggests frequency is due to UTI or calculi. Prior pelvic surgery suggests incontinence. Weak urine stream, nocturia, or both suggests BPH. Urinary frequency in an otherwise healthy young patient may be due to excessive intake of alcohol or caffeinated beverages. Gross hematuria suggests UTI and calculi in younger patients and cancer in older patients.

Testing: All patients require urinalysis and culture, which are easily done and can detect infection and hematuria.

[Table 228-12. Some Causes of Urinary Frequency]

Cytoscopy, cystometry, and urethrography can be done to diagnose cystitis, bladder outlet obstruction, and cystocele. Prostate-specific antigen level determination, ultrasonography, and prostate biopsy may be required, especially in older men, to differentiate BPH from prostate cancer.

Treatment

Treatment varies by cause.

Geriatrics Essentials

Urinary frequency in elderly men is often caused by bladder neck obstruction secondary to prostate enlargement or cancer. These patients usually require postvoid residual urine volume determination. UTI or use of diuretics may be a cause in both sexes.

Key Points

• UTI is the most common cause in children and women.

• Prostate disease is a common cause in men > 50 yr.

• Excessive intake of caffeine can cause urinary frequency in healthy people.

Chapter 229. Male Reproductive Endocrinology

Introduction

Male sexual development and function depend on a complex feedback circuit involving the hypothalamus, pituitary, and testes. Male sexual dysfunction can be secondary to hypogonadism or numerous other disorders.

Physiology

The hypothalamus produces gonadotropin-releasing hormone (GnRH), which is released in a pulsatile fashion every 60 to 120 min. The anterior pituitary responds to each pulse of GnRH by producing a corresponding pulse of luteinizing hormone (LH) and, to a lesser degree, follicle-stimulating hormone (FSH). Continuous stimulation by GnRH (as might occur therapeutically) suppresses pituitary release of LH and FSH.

The Leydig cells of the testes respond to LH by producing between 5 and 10 mg of testosterone daily. Testosterone levels are highest in early morning, except in older men, who may lose circadian variation.

Testosterone is synthesized from cholesterol through several intermediate compounds, including dehydroepiandrosterone (DHEA) and androstenedione. Circulating testosterone is mostly protein-bound, about 40% to sex hormone-binding globulin (SHBG) and 58% to albumin. Because testosterone is avidly bound to SHBG, only albumin-bound testosterone (which is less avidly bound) and the 1 to 2% that constitute free testosterone are bioavailable.

In target tissues, about 4 to 8% of testosterone is converted to a more potent metabolite, dihydrotestosterone (DHT), by the enzyme 5α-reductase. DHT has important trophic effects in the prostate and mediates androgenic alopecia. In adults, spermatogenesis requires adequate intratesticular testosterone, but the role of DHT in spermatogenesis is unclear.

Testosterone and DHT have metabolic effects, including increasing protein anabolism and nitrogen retention, increasing bone density and muscle mass, and modulating the immune system. Testosterone undergoes conversion to estradiol; estrogen mediates much of the effect of testosterone on organs such as bones and the brain.

Testosterone, DHT, and estradiol provide negative feedback on the hypothalamic-pituitary axis. In males, estradiol is the main inhibitor of LH production, whereas both estradiol and inhibin B, a peptide produced by Sertoli cells of the testes, inhibit production of FSH. In the presence of testosterone, FSH stimulates the Sertoli cells and induces spermatogenesis. In spermatogenesis, each germinal cell (spermatogonium), located adjacent to the Sertoli cells, undergoes differentiation into 16 primary spermatocytes, each of which generates 4 spermatids. Each spermatid matures into a spermatozoon. Spermatogenesis takes 72 to 74 days and yields about 100 million new spermatozoa each day. Upon maturation, spermatozoa are released into the rete testis, where they migrate to the epididymis and eventually to the vas deferens. Migration requires an additional 14 days. Before ejaculation, spermatozoa are mixed with secretions from the seminal vesicles, prostate, and bulbourethral glands.

Sexual Differentiation, Adrenarche, and Puberty

In the embryo, the presence of a Y chromosome triggers development and growth of the testes, which begin secreting testosterone and a mullerian duct inhibitor by about 7 wk of gestation. Testosterone virilizes the wolffian

[
Fig. 229-1. Puberty—when male sexual characteristics develop.]

duct (which develops into the epididymis, vas deferens, and seminal vesicles). DHT promotes development of the remainder of the male genitals. Testosterone levels peak in the 2nd trimester and fall to almost zero by birth. Testosterone production rises briefly during the first 6 mo of life, the function of

which is unclear. Thereafter, testosterone levels remain low until puberty.

LH and FSH are elevated at birth but fall to low levels within a few months, remaining low or undetectable throughout the prepubertal years. Through an unknown mechanism, blood levels of the adrenal androgens DHEA and DHEA sulfate begin to increase several years before puberty. Their conversion to testosterone in small amounts initiates pubic and axillary hair growth (adrenarche).

The mechanisms that initiate puberty are unclear, although early in puberty the hypothalamus becomes less sensitive to the inhibitory effects of sex hormones. This desensitization increases secretion of LH and FSH, stimulating testosterone production. Secretion of LH and FSH increases initially only during sleep; later, secretion increases throughout the 24-h period. The increased testosterone levels in boys cause pubertal changes, the first of which are growth of the testes (> 2.5 cm on the long axis, > 3 to 4 mL in volume) and thinning of scrotal skin. Later, penile length, muscle mass, and bone density increase; the voice deepens; and pubic and axillary hair becomes denser and thicker (see Fig. 229-1).

Effects of Aging

Both hypothalamic secretion of GnRH and the response of Leydig cells to FSH and LH diminish with aging. Beginning at about age 30, a man's serum total testosterone level declines by 1%/yr. Men aged 70 to 80 tend to have serum testosterone levels that are about one half to two thirds of those of men in their 20s. In addition, SHBG levels increase with aging, causing an even greater decline in serum free and bioavailable testosterone. FSH and LH levels tend to be normal or high-normal. These age-related changes are sometimes referred to as the andropause, although there are no abrupt changes in hormone levels as occur in the menopause. The decline in testosterone may contribute to age-related muscle loss, osteopenia, loss of libido, and cognitive decline. Testosterone supplementation for men with low-normal levels of testosterone is controversial. Some experts recommend a trial of testosterone supplementation in older men with symptoms or signs of hypogonadism and whose serum testosterone levels are below the lower limit of normal for men aged 20 to 40 yr. No data favor any of the testosterone preparations specifically for use in older men.

Male Hypogonadism

(See also p. 2891.)

Hypogonadism is defined as testosterone deficiency with associated symptoms or signs, deficiency of spermatozoa production, or both. It may result from a disorder of the testes (primary hypogonadism) or of the hypothalamic-pituitary axis (secondary hypogonadism). Both may be congenital or acquired as the result of aging, disease, drugs, or other factors. Additionally, a number of congenital enzyme deficiencies cause varying degrees of target organ androgen resistance. Diagnosis is confirmed by hormone levels. Treatment varies with etiology but typically includes testosterone replacement.

Etiology

Primary hypogonadism involves failure of the testes to respond to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). When primary hypogonadism affects testosterone production, testosterone is insufficient to inhibit production of FSH and LH; hence, FSH and LH levels are elevated. The most common cause of primary hypogonadism is Klinefelter's syndrome. It involves seminiferous tubule dysgenesis and a 47,XXY karyotype (see p. 3005).

Secondary hypogonadism is failure of the hypothalamus (or pituitary) to produce enough FSH and LH. With secondary hypogonadism, testosterone levels are low, but levels of FSH and LH are low or inappropriately normal. Any acute systemic illness can cause temporary secondary hypogonadism. Some syndromes of hypogonadism have both primary and secondary causes (mixed hypogonadism). Table 229-1 lists some common causes of hypogonadism by category.

Some syndromes of hypogonadism (eg, cryptorchidism, some systemic disorders) affect spermatozoon production more than testosterone levels.

Symptoms and Signs

Age at onset of testosterone deficiency dictates the clinical presentation: congenital, childhood-onset, or adult-onset hypogonadism. Congenital hypogonadism may be of 1st-, 2nd-, or 3rd-trimester onset.

First-trimester onset results in inadequate male sexual differentiation. Complete absence of testosterone's effects results in normal-appearing female external genitals. Partial testosterone deficiency results in abnormalities ranging from ambiguous external genitals to hypospadias. Second- or 3rd-trimester onset of testosterone deficiency results in microphallus and undescended testes.

Childhood-onset testosterone deficiency (see p. 2891) has few consequences and usually is unrecognized until puberty is delayed. Untreated hypogonadism impairs development of secondary sexual characteristics. As adults, affected patients have poor muscle development, a high-pitched voice, a small scrotum, decreased phallic and testicular growth, sparse pubic and axillary hair, and an absence of body hair. They may develop gynecomastia and eunuchoidal body proportions (span > height by 5 cm and pubic to floor

[**Table 229-1.** Causes of Hypogonadism*]

length > crown to pubic length by > 5 cm) because of delayed fusion of the epiphyses and continued long bone growth.

Adult-onset testosterone deficiency has varied manifestations depending on the degree and duration of the deficiency. Decreased libido; erectile dysfunction; decline in cognitive skills, such as visual-spatial interpretation; sleep disturbances; vasomotor instability (in acute, severe male hypogonadism); and mood changes, such as depression and anger, are common. Decreased lean body mass, increased visceral fat, testicular atrophy, osteopenia, gynecomastia, and sparse body hair typically take months to years to develop. Testosterone deficiency may increase the risk of coronary artery disease.

Diagnosis

• Testing, beginning with FSH, LH, and testosterone levels

Congenital and childhood-onset hypogonadism are often suspected because of developmental abnormalities or delayed puberty. Adult-onset hypogonadism should be suspected on the basis of symptoms or signs but is easily missed because these markers are insensitive and nonspecific. Klinefelter's syndrome should be considered in adolescent males in whom puberty is delayed, young men with hypogonadism, and all adult men with very small testes. Hypogonadism requires confirmatory testing (see
Fig. 229-2).

Diagnosis of primary and secondary hypogonadism: Increases in FSH and LH are more sensitive for primary hypogonadism than are decreases in testosterone levels. Levels of FSH and LH also help determine whether hypogonadism is primary or secondary; high gonadotropin levels, even with low-normal testosterone levels, indicate primary hypogonadism, whereas gonadotropin levels that are low or lower than expected for the level of testosterone indicate secondary hypogonadism. Alternatively, in boys of short stature with delayed puberty, low testosterone plus low gonadotropin levels might result from constitutional delay of puberty. Elevation of serum FSH with normal levels of serum testosterone and LH often occurs when spermatogenesis is impaired but testosterone production is normal. The cause of hypogonadism is often evident clinically. Primary hypogonadism requires no further testing, although some clinicians do a karyotype to definitively diagnose Klinefelter's syndrome.

Total (or calculated free and weakly bound) serum testosterone, serum FSH, and serum LH levels are measured simultaneously. The normal range for total testosterone is 300 to 1000 ng/dL (10.5 to 35 nmol/L). The initial screening testosterone level may be done at any time of day, but a second testosterone level should be drawn in the morning to confirm hypogonadism. Because of the increase in sex hormone-binding globulin (SHBG) with aging, total testosterone level is less sensitive for

hypogonadism after age 50. Although serum free testosterone more accurately reflects functional testosterone levels, its measurement requires equilibrium dialysis, which is technically difficult and not widely available. Some commercially available kits, including the analog free testosterone assay, attempt to measure serum free testosterone levels, but the results are often inaccurate, particularly in conditions such as type 2 diabetes, obesity, and hypothyroidism that alter SHBG levels. Free testosterone levels can be calculated based on SHBG, albumin, and testosterone values: there are calculators available online. Because of the pulsatile secretion of FSH and LH, they are sometimes measured as a pooled sample of 3 venipunctures taken at 20-min intervals, but these pooled samples seldom add clinically important information compared with a single blood sample. Serum FSH and LH levels are usually ≤ 5 mIU/mL before puberty and between 5 and 15 mIU/mL in adulthood.

Sperm count can be useful and should be assessed in men who are seeking fertility treatment. In adolescents or adults, a semen sample collected by masturbation after 2 days of abstinence from ejaculation provides an excellent index of seminiferous tubular function. A normal semen sample has a volume of > 2.5 mL with > 20 million sperm/mL, of which 60% are of normal morphology and are motile (see also p. 2592).

Evaluation of secondary hypogonadism: Because any systemic illness can temporarily decrease levels of testosterone, FSH, and LH, secondary hypogonadism should be confirmed by measuring these levels again after at least a 4-wk interval after resolution of the systemic illness. To confirm secondary hypogonadism in adolescents, the gonadotropin-releasing hormone (GnRH) test is sometimes done. If, in response to IV GnRH, levels of FSH and LH increase, puberty is simply delayed. If levels do not increase, true hypogonadism is likely.

To help determine the cause of confirmed secondary hypogonadism, testing should

[**Fig. 229-2.** Laboratory evaluation of male hypogonadism.]

include serum prolactin level and transferrin saturation (to screen for hemochromatosis—see p. 1032). Sella imaging with MRI or CT is done to exclude a pituitary macroadenoma or other mass in men < 60 yr with no other identified cause for hypogonadism and in all men with very low total testosterone levels (< 200 ng/dL), elevated prolactin levels, or symptoms consistent with a pituitary tumor (eg, headache, visual symptoms). Also, if there are symptoms or signs of Cushing's syndrome, 24-h urine collection for free cortisol or a dexamethasone suppression test is done (see p. 797). If no abnormalities are identified, the diagnosis is acquired idiopathic secondary hypogonadism.

Treatment

• Testosterone therapy

• Gonadotropin replacement therapy for restoration of fertility due to secondary hypogonadism

Treatment is directed toward providing adequate androgen replacement conveniently and safely. Although patients with primary hypogonadism will not become fertile with any endocrine therapy, patients with secondary hypogonadism often become fertile with gonadotropin therapy. Testosterone formulations discussed here are those available in the US. Other formulations may be available in other countries.

Testosterone therapy: Males who have no signs of puberty and are near age 15 may be given long-acting testosterone enanthate 50 mg IM once/mo for 4 to 8 mo. These low doses cause some virilization without restricting adult height. Older adolescents with testosterone deficiency receive long-acting testosterone enanthate or cypionate at a dose that is increased gradually over 18 to 24 mo from 50 to 100 to 200 mg IM q 1 to 2 wk. Transcutaneous gel may also be used, although it is more expensive, could possibly be transferred to others during intimate contact, and is more difficult to accurately dose. It is reasonable to convert older adolescents to testosterone gel 1% at adult dosages when their IM dosage has reached the equivalent of 100 to 200 mg q 2 wk.

Adults with established testosterone deficiency may benefit from replacement therapy. Treatment prevents or attenuates osteopenia, muscle loss, vasomotor instability, loss of libido, and occasionally erectile

dysfunction. Although the effects of testosterone on coronary artery disease are not completely understood, testosterone replacement therapy may improve coronary artery blood flow and may decrease the risk of coronary artery disease. Options for replacement therapy include testosterone gel 1% (5 to 10 g daily to deliver 5 to 10 mg daily), IM testosterone enanthate or cypionate (100 mg q 7 days or 200 mg q 10 to 14 days), a buccal mucosal patch (30 mg bid), or a transdermal testosterone patch (5 to 10 mg daily). Testosterone gel maintains physiologic blood levels more consistently than other treatments, but IM or patch systems are sometimes used because of their lower cost.

Potential adverse effects of testosterone and its analogs include erythrocytosis (particularly in men > 50 yr receiving IM testosterone), acne, gynecomastia, and very rarely prostatic enlargement or edema; prostatic obstructive symptoms are rare. Treatment may enhance growth of an existing prostate carcinoma and theoretically may awaken a dormant prostate cancer. Injectable or transdermal forms of testosterone are preferable to most oral formulations, which, except for testosterone undecanoate, carry a significant risk of hepatocellular dysfunction and hepatic adenoma.

Hct should be checked every 6 to 12 mo. Digital rectal examination and serum prostate-specific antigen (PSA) testing should be offered every 6 mo. If Hct is ≥ 54%, the testosterone dose should be reduced by one fourth or one third. Because the effect of testosterone replacement on PSA levels is not clear, significant increases in PSA level should prompt consideration of prostate biopsy in men who would otherwise be candidates for prostate cancer diagnosis and treatment.

Treatment of infertility due to hypogonadism: Infertility, which has many possible causes other than hypogonadism, is discussed in full elsewhere (see p. 2592). Infertility due to primary hypogonadism does not respond to hormonal therapy. Men with primary hypogonadism occasionally have a few intratesticular sperm that can be harvested with various microsurgical techniques and used to fertilize an egg by an assisted reproductive technique (eg, intracytoplasmic injection).

Infertility due to secondary hypogonadism usually responds to gonadotropin replacement therapy. Other symptoms of secondary hypogonadism respond well to testosterone replacement therapy alone. If secondary hypogonadism results from pituitary disease, gonadotropin replacement therapy usually is successful. Therapy begins with LH replacement. After all exogenous androgens are stopped, LH replacement is generally initiated using human chorionic gonadotropin (hCG). Doses begin at 375 to 750 IU sc 2 to 3 times/wk and are increased if necessary to 1000 to 2000 IU sc 2 to 3 times/wk. The dose is adjusted after 3 mo to achieve normal serum testosterone levels. Sperm counts are done monthly, but counts are not expected to increase for at least 4 mo. FSH replacement, which is expensive, begins if 6 to 12 mo of LH replacement does not stimulate spermatogenesis. FSH replacement uses human menotropic gonadotropin or human recombinant FSH, beginning with 75 to 150 IU 3 times/wk. The dose may be doubled if conception has not occurred within 6 mo of combination therapy with hCG. Many men become fertile with treatment despite sperm counts that do not usually result in fertility (eg, < 5 million/mL).

Secondary hypogonadism due to a hypothalamic defect (eg, Kallmann syndrome) is treated initially with LH and FSH because of their ready availability; if these treatments are ineffective, GnRH replacement therapy (q 2 h sc by a programmable minipump) might be more effective. Most (80 to 90%) of men respond successfully to these regimens.

Male Sexual Dysfunction

Male sexual dysfunction is a problem with 1 of the 4 main components of male sexual function (libido, erection, ejaculation, orgasm) that interferes with interest in or ability to engage in sexual intercourse. Many drugs and numerous physical and psychologic disorders affect sexual function.

Libido: Libido is the conscious component of sexual function. Decreased libido manifests as a lack of sexual interest or a decrease in the frequency and intensity of sexual thoughts, either spontaneous or in response to erotic stimuli. Libido is sensitive to testosterone levels as well as to general nutrition, health, and drugs. Conditions particularly likely to decrease libido include hypogonadism (see p. 2340), uremia, and depression. Drugs that sometimes decrease libido include weak androgen receptor antagonists, such as spironolactone or cimetidine, and virtually all drugs that are active in the CNS, such as SSRIs, tricyclic antidepressants, and antipsychotics. Loss of libido due to SSRIs or tricyclic anti-depressants sometimes

is reversible with the addition of bupropion or trazodone.

Erection: Erection occurs as the result of a complex neuropsychologic process. Higher cortical input and a sacrally mediated parasympathetic reflex arc combine to stimulate erection. Nerve output travels through the pudendal nerves, which traverse the posterolateral aspect of the prostate. Terminating in the penis, these nonadrenergic, noncholinergic nerves activate nitric oxide synthase, producing nitric oxide, which relaxes smooth muscle lining the sinusoidal spaces that connect the arterioles and venules within the corpus cavernosa. The blood flow within the sinusoids increases markedly, distending them and compressing the venules, causing veno-occlusion. The increased inflow and veno-occlusion together produce penile rigidity. Many factors affect the ability to have an erection (see below).

Ejaculation and orgasm: Ejaculation is controlled by the sympathetic nervous system. α-Adrenergic stimulation causes contractions of the epididymis, vas deferens, prostate, and muscles of the pelvic floor. In addition, the neck of the bladder closes, preventing retrograde ejaculation of semen into the bladder. SSRIs may delay or inhibit ejaculation.

Orgasm is the highly pleasurable sensation that occurs in the brain generally simultaneously with ejaculation. Anorgasmia may be a physical phenomenon due to decreased penile sensation (eg, from neuropathy) or a neuropsychologic phenomenon due to psychiatric disorders or psychoactive drugs.

Ejaculatory insufficiency is reduced or absent semen volume that may result from retrograde ejaculation or interruption of sympathetic stimulation. Retrograde ejaculation is common in men with diabetes and can also be caused by surgery on the neck of the bladder or transurethral resection of the prostate. Sympathetic interruption, either from surgery or with drugs (eg, guanethidine, phentolamine, phenoxybenzamine, thioridazine), diminishes ejaculatory volume.

Premature ejaculation is ejaculation occurring sooner than desired by the man or his partner. It is usually caused by sexual inexperience, anxiety, and other psychologic factors instead of disease. It can be treated successfully with sex therapy and SSRIs.

Erectile Dysfunction

(Impotence)

Erectile dysfunction (ED) is the inability to attain or sustain an erection satisfactory for sexual intercourse. Most erectile dysfunction is related to vascular, neurologic, psychologic, and hormonal disorders; drug use can also be a cause. Evaluation typically includes screening for underlying disorders and measuring testosterone levels. Treatment options include oral phosphodiesterase inhibitors or apomorphine, intraurethral or intracavernosal prostaglandins, mechanical pump devices, and surgical implants.

The term impotence has been replaced by the term erectile dysfunction. In the US, at least 10 to 20 million men > 18 are affected. The prevalence of partial or complete ED is about 50% in men 40 to 70 and increases with aging. However, many men can be successfully treated.

Etiology

Primary ED (ie, the man has never been able to attain or sustain erections) is rare and is almost always due to psychologic factors (guilt, fear of intimacy, depression, severe anxiety) or clinically obvious anatomic abnormalities. Most often, ED is secondary (ie, a man who previously could attain and sustain erections no longer can). Over 80% of secondary ED cases have an organic etiology. However, in many men with organic disease, ED leads to secondary psychologic difficulties that compound the problem. Psychologic factors must be considered in every case.

Psychologic causes may relate to performance anxiety, stress, or a mood disorder (particularly depression). ED may be situational, involving a particular place, time, or partner.

The major organic causes of ED are vascular and neurologic disorders, often stemming from

atherosclerosis and diabetes. Complications of surgery, usually prostate surgery, are another common cause. Other causes include hormonal disorders, drugs, and structural disorders of the penis (eg, Peyronie's disease).

The most common vascular cause is atherosclerosis of penile arteries, often secondary to diabetes. Atherosclerosis and aging decrease the capacity for dilation of arterial blood vessels and smooth muscle relaxation, limiting the amount of blood that can enter the penis. Inadequate impedance of venous outflow (venous leaks) may cause ED or, more commonly, failure to maintain tumescence as long as desired. Venous leaks make it difficult for blood to remain in the penis during erection, so erections occur but cannot be sustained. Priapism, particularly as in sickle cell disease, may damage penile vasculature and lead to ED.

Stroke, partial complex seizures, multiple sclerosis, peripheral and autonomic neuropathies, and spinal cord injuries are among the neurologic causes. Diabetic neuropathy and surgical injury are particularly common causes.

Any endocrinopathy associated with testosterone deficiency (hypogonadism) may decrease libido and cause ED. However, erectile function only rarely improves with normalization of serum testosterone levels.

Numerous drug causes are possible (see Table 229-2). Alcohol can cause temporary ED.

Of men who have undergone transurethral resection of the prostate, up to 40% can experience problems with erections for reasons that are not clear. ED is more common after more extensive prostatic resection (eg, radical prostatectomy). Prolonged perineal pressure (as occurs during bicycle riding) can cause temporary ED.

Diagnosis

• Clinical evaluation

• Screening for depression

• Testosterone level

Evaluation should include history of drug and alcohol use, smoking, diabetes, hypertension, and atherosclerosis and symptoms of vascular, hormonal, neurologic, and psychologic disorders. It is vital to screen for depression, which may not always be apparent. The Beck Depression Scale or, in older men, the Yesavage Geriatric Depression Scale (see Table 307-7 on p. 3089) is easy to administer and may be useful. Satisfaction with sexual relationships should also be explored. Partner sexual dysfunction (eg, atrophic vaginitis, depression) must be considered and evaluated.

Examination is focused on the genitals and extragenital signs of hormonal, neurologic, and vascular disorders. Genitals are examined for anomalies, signs of hypogonadism, and fibrous bands or plaques (Peyronie's disease). Poor rectal tone, perineal sensation, or abnormal anal wink or bulbocavernosus reflexes may indicate neurologic dysfunction. Diminished peripheral pulses suggest vascular dysfunction.

A psychologic cause should be suspected in young healthy men with abrupt onset of ED, particularly if onset is associated with a specific emotional event or if the dysfunction occurs only in certain settings. A history of ED with spontaneous improvement also suggests psychologic origin (psychogenic ED). Men with psychogenic ED usually have normal nocturnal erections and erections upon awakening, whereas men with organic ED often do not.

Laboratory assessment should include measurement of testosterone level; if the level is low or low-normal, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) should be measured (see p. 2342). Evaluation for occult diabetes, dyslipidemias, hyperprolactinemia, thyroid disease, and Cushing's

syndrome should be done based on clinical suspicion.

[Table 229-2. Commonly Used Drugs that Can Cause Erectile Dysfunction]

A penile pressure-brachial pressure index (systolic BP in the penis divided by systolic BP in the arm) < 0.6 indicates impaired blood flow to the penis, but this test is seldom done in general clinical practice. Additional invasive or provocative penile tests include duplex ultrasonography before and after injection of a vasoactive drug and cavernosography or cavernosometry; these tests can be considered in some patients, such as those with posttraumatic erectile dysfunction or before penile reconstructive surgery (eg, for Peyronie's disease).

Treatment

• Treatment of cause

• Usually an oral phosphodiesterase inhibitor

• Sometimes a mechanical device or an intracavernosal or intraurethral prostaglandin

Underlying organic disorders require appropriate treatment. Drugs that are temporally related to onset of ED should be stopped or switched. Depression may require treatment. For all patients, reassurance and education (including of the patient's partner whenever possible) are important.

For further therapy, noninvasive methods (mechanical devices and drugs) are tried first. All drugs and devices should be tried ≥ 5 times before being considered ineffective.

Mechanical devices: Men who can develop but not sustain an erection may use a constriction ring. As soon as erection occurs, a metal or elastic ring or a leather band with snaps (sold by prescription in pharmacies or OTC in sex paraphernalia stores as a "cock ring") is placed around the base of the penis, preventing venous outflow. If the man cannot develop an erection, a vacuum device can draw blood into the penis, after which the band or ring is placed at the base of the penis to retain the erection. Bruising of the penis, coldness of the tip of the penis, and lack of spontaneity are some drawbacks to this modality. A constriction ring and vacuum devices might also be useful adjuncts for patients who do not respond satisfactorily to drug therapy.

Drugs: The primary drugs for ED are oral phosphodiesterase inhibitors, oral apomorphine (not available in the US), and intracavernosal or intraurethral prostaglandins. Almost all patients prefer oral drug therapy to other methods for treating ED.

Oral phosphodiesterase inhibitors selectively inhibit cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), the predominant phosphodiesterase isoform in the penis. These drugs include sildenafil, vardenafil, and tadalafil. By increasing cGMP, these drugs enhance the nitric oxide release essential for normal erection. Although vardenafil and tadalafil are more selective for the penile vasculature than sildenafil, adverse effects of these drugs are similar. Although no clinical trials directly compare the drugs, all 3 appear to be equally effective (60 to 75%). Sildenafil dose is 50 mg, although most men respond best to 100 mg. Tadalafil has a significantly longer half-life (24 to 48 h) than sildenafil and vardenafil (about 4 to 6 h), which might lead to more convenient dosing. The usual dosage for tadalafil and vardenafil is 5 to 20 mg. All PDE5 inhibitors are generally taken at least 1 h before sexual intercourse. Dosing frequency should not be ≤ 24 h for sildenafil and vardenafil and not ≤ 48 h for tadalafil. All PDE5 inhibitors cause direct coronary vasodilation and potentiate the hypotensive effects of other nitrates, including those used to treat cardiovascular disease as well as recreational amyl nitrate ("poppers"). Thus, all nitrates are contraindicated for 24 h after the administration of any PDE5 inhibitor. Other adverse effects of PDE5 inhibitors include flushing, visual abnormalities, and headache. Sildenafil and vardenafil may cause abnormal color perception. Tadalafil use has been linked with myalgias. Some users of PDE5 inhibitors have rarely developed anterior ischemic optic neuropathy, but whether there is a causal relationship is unclear. Vardenafil should be administered cautiously and at lower initial dosages to patients receiving α-blockers, such as prazosin, doxazosin, and tamsulosin, because of the risk of prolonged hypotension. One study showed that sildenafil may be safely administered with doxazosin.

Apomorphine increases erectile neurogenic signals by CNS mechanisms. It appears to be only moderately effective and can cause nausea, somnolence, and hypotension.

Alprostadil (the prostaglandin PGE_1), given via intraurethral insertion or intracavernosal injection, can produce erections with a mean duration of about 60 min. It causes priapism (see p. 2327) in ≤ 1% and penile pain in about 10%. The intracavernosal dose is adjusted by the physician to minimize priapism; the patient can then self-inject at home. Priapism is less common with intraurethral therapy, but intraurethral therapy is much less effective (50 to 60%) than intracavernosal injection, the most effective pharmacotherapy for erectile dysfunction (80 to 90%). Combination therapy with a PDE5 inhibitor and alprostadil may be useful for some patients who fail to respond to oral PDE5 inhibitors alone.

Surgery: For patients who do not respond to drug therapy, invasive treatment options include implantation of a penile prosthesis. Prostheses can be rigid plastic rods or hydraulically operated devices. Both involve the risks of general anesthesia, infection, and prosthetic malfunction.

Gynecomastia

Gynecomastia is hypertrophy of breast glandular tissue in males. It must be differentiated from pseudogynecomastia, which is increased breast fat, but no enlargement of breast glandular tissue.

Pathophysiology

During infancy and puberty, enlargement of the male breast is normal (physiologic gynecomastia). Enlargement is usually transient, bilateral, smooth, firm, and symmetrically distributed under the areola; breasts may be tender. Physiologic gynecomastia that develops during puberty usually resolves within about 6 mo to 2 yr. Similar changes may occur during old age and may be unilateral or bilateral. Most of the enlargement is due to proliferation of stroma, not of breast ducts. The mechanism is usually a decrease in androgen effect or an increase in estrogen effect (eg, decrease in androgen production, increase in estrogen production, androgen blockade, displacement of estrogen from sex-hormone binding globulin, androgen receptor defects).

If evaluation reveals no cause for gynecomastia, it is considered idiopathic. The cause may not be found because gynecomastia is physiologic or because there is no longer any evidence of the inciting event.

Etiology

In infants and boys, the most common cause is

• Physiologic gynecomastia

In men, the most common causes are (see Table 229-3)

• Persistent pubertal gynecomastia

• Idiopathic gynecomastia

• Drugs (particularly spironolactone, anabolic steroids, and antiandrogens—see Table 229-4)

Breast cancer, which is uncommon in males, may cause unilateral breast abnormalities but is rarely confused with gynecomastia.

Evaluation

History: History of present illness should help clarify the duration of breast enlargement, whether secondary sexual characteristics are fully developed, the relationship between onset of gynecomastia

and puberty, and the presence of any genital symptoms (eg, decreased libido, erectile dysfunction) and breast symptoms (eg, pain, nipple discharge).

Review of systems should seek symptoms that suggest possible causes, such as weight loss and fatigue (cirrhosis, undernutrition, chronic kidney disease, hyperthyroidism); skin discoloration (chronic kidney disease, cirrhosis); hair loss and frequent infections (undernutrition); fragility fractures (undernutrition, hypogonadism); mood and cognitive changes (hypogonadism); and tremor, heat intolerance, and diarrhea (hyperthyroidism).

Past medical history should address disorders that can cause gynecomastia and include a history of all prescribed and OTC drugs.

Physical examination: Complete examination is done, including assessment of vital signs, skin, and general appearance. The neck is examined for goiter. The abdomen is examined for ascites, venous distention, and suspected adrenal masses. Development of secondary sexual characteristics (eg, the penis, pubic hair, and axillary hair) is assessed. The testes are examined for masses and atrophy.

The breasts are examined while patients are recumbent with their hands behind their head. Examiners bring their thumb and forefinger together from opposite sides of the nipple until they meet. Lumps are assessed and characterized in terms of location, consistency, fixation to underlying tissues, and skin changes. The

[Table 229-3. Some Causes of Gynecomastia]

axilla is examined for lymph node involvement in men who have breast lumps.

Red flags: The following findings are of particular concern:

- Localized or eccentric breast swelling, particularly with nipple discharge, fixation to the skin, or hard consistency
- Symptoms or signs of hypogonadism
- Symptoms or signs of hyperthyroidism
- Testicular mass
- Recent onset of painful, tender gynecomastia in an adult

Interpretation of findings: With pseudogynecomastia, the examiner feels no resistance between the thumb and forefinger until they meet at the nipple. In contrast, with gynecomastia, a rim of tissue > 0.5 cm in diameter surrounds the nipple symmetrically and is

[Table 229-4. Common Drug Causes of Gynecomastia*]

similar in consistency to the nipple itself. Breast cancer is suggested by swelling with any of the following characteristics:

- Eccentric unilateral location
- Firm or hard consistency
- Fixation to skin or fascia
- Nipple discharge
- Skin dimpling

• Nipple retraction

• Axillary lymph node involvement

Gynecomastia in an adult that is of recent onset and causes pain is more often caused by a hormonal abnormality (eg, tumor, hypogonadism) or drugs. Other examination findings may also be helpful (see Table 229-5).

Testing: If breast cancer is considered, mammography should be done. If another disorder is suspected, appropriate testing should be done (see Table 229-3). Extensive testing is often unnecessary, especially for patients in whom the gynecomastia is chronic and detected only on physical examination. Because hypogonadism is somewhat common with aging, some authorities recommend measuring the serum testosterone level in older men, particularly if other findings suggest hypogonadism. However, in adults with recent onset of painful gynecomastia without a drug or evident pathologic cause, measurement of serum levels of LH, FSH, testosterone, estradiol and human chorionic gonadotropin (hCG) are recommended. Patients with physiologic or idiopathic gynecomastia are evaluated again in 6 mo.

Treatment

In most cases, no specific treatment is needed because gynecomastia usually remits spontaneously or disappears after any causative drug (except perhaps anabolic steroids) is stopped or underlying disorder is treated. Some clinicians try tamoxifen 10 mg po bid if pain and tenderness are very troublesome in men or adolescents, but this treatment is not always effective. Tamoxifen may also help prevent gynecomastia in men being treated with high-dose antiandrogen (eg, bicalutamide) therapy for prostate cancer; breast radiation therapy is an alternative. Resolution of gynecomastia is unlikely after 12 mo. Thus, after 12 mo, if cosmetic appearance is unacceptable, surgical removal of excess breast tissue (eg, suction lipectomy alone or with cosmetic surgery) may be used.

Key Points

• Gynecomastia must be differentiated from increased fat tissue in the breast.

• Gynecomastia is often physiologic or idiopathic.

• A wide variety of drugs can cause gynecomastia.

• Patients should be evaluated for clinically suspected genital or systemic disorders.

[**Table 229-5.** Interpretation of Some Findings in Gynecomastia]

Chapter 230. Voiding Disorders

Introduction

Voiding disorders affect urine storage or release because both are controlled by the same neural and urinary tract mechanisms. The result is incontinence or retention.

For normal urinary function, the autonomic and voluntary nervous systems must be intact, and muscles of the urinary tract must be functional. Normally, bladder filling stimulates stretch receptors in the bladder wall to send impulses via spinal nerves S2 to S4 to the spinal cord, then to the sensory cortex, where the need to void is perceived. A threshold volume, which differs from person to person, triggers awareness of the need to void. However, the external urinary sphincter at the bladder outlet is under voluntary control and usually remains contracted until a person decides to urinate. The micturition inhibitory center in the frontal lobe also helps control urination. When the decision is made, voluntary signals in the motor cortex initiate urination. These impulses are transmitted to the pontine micturition center, which coordinates simultaneous signals to contract detrusor smooth muscle throughout the bladder (via parasympathetic cholinergic nerve fibers) and to relax the internal sphincter (via alpha sympathetic nerve fibers) and striated muscle of the external sphincter and pelvic floor (see Fig. 230-1). In addition to normal urinary function, continence and normal voiding require normal cognitive function (including motivation), mobility, access to a toilet, and manual dexterity.

Damage to or dysfunction of any of the components involved in voiding can cause urinary incontinence or retention.

Urinary Incontinence

(See also Incontinence in Children on p. 2923)

Urinary incontinence is involuntary loss of urine; some experts consider it present only when a patient thinks it is a problem. The disorder is greatly underrecognized and under-reported. Many patients do not report the problem to their physician, and many physicians do not ask about incontinence specifically. Incontinence can occur at any age but is more common among the elderly and among women, affecting about 30% of elderly women and 15% of elderly men.

Incontinence greatly reduces quality of life by causing embarrassment, stigmatization, isolation, and depression. Many elderly patients are institutionalized because incontinence is a burden to caregivers. In bedbound patients, urine irritates and macerates skin, contributing to sacral pressure ulcer formation. Elderly people with urgency are at increased risk of falls and fractures.

Types: Incontinence may manifest as near-constant dribbling or as intermittent voiding with or without awareness of the need to void. Some patients have extreme urgency (irrepressible need to void) with little or no warning and may be unable to inhibit voiding until reaching a bathroom. Incontinence may occur or worsen with maneuvers that increase intra-abdominal pressure. Postvoid dribbling is extremely common and probably a normal variant in men. Identifying the clinical pattern is sometimes useful, but causes often overlap and much of treatment is the same.

Urge incontinence is uncontrolled urine leakage (of moderate to large volume) that occurs immediately after an urgent, irrepressible need to void. Nocturia and nocturnal incontinence are common. Urge incontinence is the most common type of incontinence in the elderly but may affect younger people. It is often precipitated by use of a diuretic and is exacerbated by inability to quickly reach a bathroom. In women, atrophic vaginitis, common with aging, contributes to thinning and irritation of the urethra and urgency.

Stress incontinence is urine leakage due to abrupt increases in intra-abdominal pressure (eg, with coughing, sneezing, laughing, bending, or lifting). Leakage volume is usually low to moderate. It is the 2nd most common type of incontinence in women, largely because of complications of childbirth and development of atrophic urethritis. Stress incontinence is typically more severe in obese people because of pressure from abdominal contents on the top of the bladder.

Overflow incontinence is dribbling of urine from an overly full bladder. Volume is usually small, but leaks may be constant, resulting in large total losses. Overflow incontinence is the 2nd most common type of incontinence in men.

Functional incontinence is urine loss due to cognitive or physical impairments (eg, due to dementia or stroke) or environmental barriers that interfere with control of voiding. For example, the patient may not recognize the need to void, may not know where the toilet

[Fig. 230-1. Normal micturition occurs when bladder contraction is coordinated with urethral sphincter relaxation.]

is, or may not be able to walk to a remotely located toilet. Neural pathways and urinary tract mechanisms that maintain continence may be normal.

Mixed incontinence is any combination of the above types. The most common combinations are urge with stress incontinence and urge or stress with functional incontinence.

Etiology

The disorder tends to differ among age groups. With aging, bladder capacity decreases, ability to inhibit urination declines, involuntary bladder contractions (detrusor overactivity) occur more often, and bladder contractility is impaired. Thus, voiding becomes more difficult to postpone and tends to be incomplete. Postvoid residual volume increases, probably to ≤ 100 mL (normal < 50 mL). Endopelvic fascia weakens. In postmenopausal women, decreased estrogen levels lead to atrophic urethritis and atrophic vaginitis and to decreasing urethral resistance, length, and maximum closure pressure. In men, prostate size increases, partially obstructing the urethra and leading to incomplete bladder emptying and strain on the detrusor muscle. These changes occur in many normal, continent elderly people and may facilitate incontinence but do not cause it.

In younger patients, incontinence often begins suddenly, may cause little leakage, and usually resolves quickly with little or no treatment. Often, incontinence has one cause in younger patients but has several in the elderly.

Conceptually, categorization into reversible (transient) or established causes may be useful. However, causes and mechanisms often overlap and occur in combination.

Transient incontinence: There are several causes of transient incontinence (see Table 230-1). A useful mnemonic for many transient causes is DIAPPERS (with an extra P): *D*elirium, *I*nfection (commonly, symptomatic UTIs), *A*trophic urethritis and vaginitis, *P*harmaceuticals (eg, those with α-adrenergic, cholinergic, or anticholinergic properties; diuretics; sedatives), *P*sychiatric disorders (especially depression), *E*xcess urine output (polyuria), *R*estricted mobility, and *S*tool impaction.

Established incontinence: Established incontinence is caused by a persistent problem affecting nerves or muscles. Mechanisms usually used to describe these problems are bladder outlet incompetence or obstruction, detrusor overactivity or underactivity, detrusor-sphincter dyssynergia, or a combination (see Table 230-2). However, these mechanisms are also involved in some transient causes.

Outlet incompetence is a common cause of stress incontinence. In women, it is usually due to weakness of the pelvic floor or of the endopelvic fascia. Such weakness commonly results from multiple vaginal deliveries, pelvic surgery (including hysterectomy), age-related changes (including atrophic urethritis), or a combination. As a result, the vesicourethral junction descends, the bladder neck and urethra become hypermobile, and pressure in the urethra falls below that of the bladder. In men, a common cause is damage to the sphincter or to the bladder neck and posterior urethra after radical prostatectomy.

Outlet obstruction is a common cause of incontinence in men, although most men with obstruction are not incontinent. Obstruction in men commonly results from benign prostatic hyperplasia, prostate cancer,

or urethral stricture. In women, outlet obstruction is rare but can result from previous surgery for incontinence or from a prolapsed cystocele that causes the urethra to kink during straining to void. In both sexes, fecal impaction can cause obstruction. Obstruction leads to a chronically overdistended bladder, which loses its ability to contract; then the bladder does not empty completely, resulting in overflow. Obstruction also may lead to detrusor overactivity and urge incontinence. If the detrusor muscle loses its ability to contract, overflow incontinence may follow. Some causes of outlet obstruction (eg, large bladder diverticula, cystoceles, bladder infections, calculi, and tumors) are reversible.

Detrusor overactivity is a common cause of urge incontinence in elderly and younger patients. The detrusor muscle contracts intermittently for no apparent reason, usually when the bladder is partially or nearly full. Detrusor overactivity may be idiopathic or may result from dysfunction of the frontal micturition inhibitory center (commonly due to age-related changes, dementia, or stroke) or outlet obstruction. Detrusor overactivity (hyperactivity) with impaired contractility (DHIC) is a variant of urge incontinence characterized by urgency, frequency, a weak flow rate, urinary retention, bladder trabeculation, and a postvoid residual volume of > 50 mL. This variant may mimic prostatism in men or stress incontinence in women.

Detrusor underactivity causes urinary retention and overflow incontinence in about 5% of patients with incontinence. It may be caused by injury to the spinal cord (see p. 3227) or to nerve roots supplying the bladder (eg, by disk compression, tumor, or surgery), by peripheral or autonomic neuropathies, or by other neurologic disorders (see Table 230-2). Anticholinergics and opioids greatly decrease detrusor contractility; these drugs are common transient causes. The detrusor may become underactive in men with chronic outlet obstruction as the detrusor is replaced by fibrosis and connective tissue, preventing the bladder from emptying even when the obstruction is removed. In women, detrusor underactivity is usually idiopathic. Less severe detrusor weakness is common among elderly women. Such weakness does not cause incontinence but can complicate treatment if other causes of incontinence coexist.

Detrusor-sphincter dyssynergia (loss of coordination between bladder contraction and external urinary sphincter relaxation) may cause outlet obstruction, with resultant overflow incontinence. Dyssynergia is often due to a spinal cord lesion that interrupts pathways to the pontine micturition center, which coordinates sphincter relaxation and bladder contraction. Rather than relaxing when the bladder contracts, the sphincter contracts, obstructing the bladder outlet. Dyssynergia causes severe trabeculation, diverticula, a "Christmas tree" deformation of the bladder, hydronephrosis, and renal failure.

Functional impairment (eg, cognitive impairment, reduced mobility, reduced manual dexterity, coexisting disorders, lack of motivation), particularly in the elderly, may contribute to established incontinence but rarely causes it.

[**Table 230-1.** Causes of Transient Incontinence]

Evaluation

- History
- Examination: neurologic, pelvic, rectal
- Testing: urinalysis, urine culture, BUN, and creatinine; postvoid residual volume; sometimes urodynamic testing

Most patients, embarrassed to mention incontinence, do not volunteer information about it, although they may mention related symptoms (eg, frequency, nocturia, hesitancy). All adults should therefore be screened with a question such as "Do you ever leak urine?"

Clinicians should not assume that incontinence is irreversible just because it is longstanding. Also, urinary retention (see p. 2362) must be excluded before treatment for detrusor overactivity is started.

History: History focuses on duration and patterns of voiding, bowel function, drug use, and obstetric and pelvic surgical history. A voiding diary can provide clues to causes. Over 48 to 72 h, the patient or

caregiver records volume and time of each void and each incontinent episode in relation to associated activities (especially eating, drinking, and drug use) and during sleep. The amount of urine leakage can be estimated as drops, small, medium, or soaking; or by pad tests (measuring the weight of urine absorbed by feminine pads or incontinence pads during a 24-h period). If the volume of most nightly voids is much smaller than functional bladder capacity (defined as the largest single voided volume recorded in the diary), the cause is a sleep-related problem (patients void because they are awake anyway) or a bladder abnormality (patients without bladder dysfunction or a sleep-related problem awaken to void only when the bladder is full).

Of men with obstructive symptoms (hesitancy, weak urinary stream, intermittency, feeling of incomplete bladder emptying), about one third have detrusor overactivity without obstruction.

Urgency or an abrupt gush of urine without warning or without preceding increase in intra-abdominal pressure (often called reflex or unconscious incontinence) typically indicates detrusor overactivity.

Physical examination: Neurologic, pelvic, and rectal examinations are the focus.

Neurologic examination involves assessing mental status, gait, and lower extremity function and checking for signs of peripheral or autonomic neuropathy, including orthostatic hypotension. Neck and upper extremities should be checked for signs of cervical spondylosis or stenosis. The spinal column should be checked for evidence of prior surgeries and for deformities, dimples, or hair tufts suggesting neural tube defects.

Innervation of the external urethral sphincter, which shares the same sacral roots as the anal sphincter, can be tested by assessing:

- Perineal sensation
- Volitional anal sphincter contraction (S2 to S4)
- The anal wink reflex (S4 to S5), which is anal sphincter contraction triggered by lightly stroking perianal skin
- The bulbocavernosus reflex (S2 to S4), which is anal sphincter contraction triggered by pressure on the glans penis or clitoris

However, the absence of these reflexes is not necessarily pathologic.

Pelvic examination in women can identify atrophic vaginitis and urethritis, urethral hypermobility, and pelvic floor weakness. Pale, thin

[**Table 230-2.** Causes of Established Incontinence]

vaginal mucosae with loss of rugae indicate atrophic vaginitis. Urethral hypermobility can be seen during coughing when the posterior vaginal wall is stabilized with a speculum. A cystocele, an enterocele, a rectocele, or uterine prolapse suggests pelvic floor weakness (see p. 2529). When the opposite wall is stabilized with a speculum, bulging of the anterior wall indicates a cystocele, and bulging of the posterior wall indicates a rectocele or enterocele. Pelvic floor weakness does not suggest a cause, unless a large, prolapsed cystocele is present.

Rectal examination can identify fecal impaction, rectal masses, and, in men, prostate nodules or masses. Prostate size should be noted but correlates poorly with outlet obstruction. Suprapubic palpation and percussion to detect bladder distention are usually of little value except in extreme acute cases of urinary retention.

If stress incontinence is suspected, urinary stress testing can be done on the examination table; it has a sensitivity and specificity of > 90%. The bladder must be full; a patient sits upright or close to upright with the legs spread, relaxes the perineal area, and coughs vigorously once. Immediate leakage that starts

and stops with the cough confirms stress incontinence. Delayed or persistent leakage suggests detrusor overactivity triggered by the cough. If cough triggers incontinence, the maneuver can be repeated while the examiner places 1 or 2 fingers inside the vagina to elevate the urethra (Marshall-Bonney test); incontinence that is corrected by this maneuver may respond to surgery. Results can be false-positive if patients have an abrupt urge to void during the test or false-negative if patients do not relax, the bladder is not full, the cough is not strong, or a large cystocele is present (in women). In the last case, the test should be repeated with the patient supine and the cystocele reduced, if possible.

Testing: Urinalysis, urine culture, and measurement of BUN and serum creatinine are required. Other tests may include serum glucose and Ca (with albumin for estimation of protein-free Ca levels) if the voiding diary suggests polyuria, electrolytes if patients are confused, and vitamin B_{12} levels if clinical findings suggest a neuropathy.

Postvoid residual volume should be determined by catheterization or ultrasonography. Postvoid residual volume plus voided volume estimates total bladder capacity and helps assess bladder proprioception. A volume < 50 mL is normal; < 100 mL is usually acceptable in patients > 65 but abnormal in younger patients; and > 100 mL may suggest detrusor underactivity or outlet obstruction.

Urodynamic testing is indicated when clinical evaluation combined with the appropriate tests is not diagnostic or when abnormalities must be precisely characterized before surgery.

Cystometry may help diagnose urge incontinence, but sensitivity and specificity are unknown. Sterile water is introduced into the bladder in 50-mL increments using a 50-mL syringe and a 12- to 14-F urethral catheter until the patient experiences urgency or bladder contractions, detected by changes in fluid level in the syringe. If < 300 mL causes urgency or contractions, detrusor overactivity and urge incontinence are likely.

Peak urinary flow rate testing with a flow meter is used to confirm or exclude outlet obstruction in men. Results depend on initial bladder volume, but a peak flow rate of < 12 mL/sec with a urinary volume of ≥ 200 mL and prolonged voiding suggest outlet obstruction or detrusor underactivity. A rate of ≥ 12 mL/sec excludes obstruction and may suggest detrusor overactivity. During testing, patients are instructed to place their hand on their abdomen to check for straining during urination, especially if stress incontinence is suspected and surgery is contemplated. Straining suggests detrusor weakness that may predispose patients to postoperative retention.

In cystometrography, pressure-volume curves and bladder sensation are recorded while the bladder is filled with sterile water; provocative testing (with bethanechol or ice water) is used to stimulate bladder contractions. Electromyography of perineal muscle is used to assess sphincter innervation and function. Urethral, abdominal, and rectal pressures may be measured. Pressure-flow video studies, usually done with voiding cystourethrography (see p. 2315), can correlate bladder contraction, bladder neck competency, and detrusor-sphincter synergy, but equipment is not widely available.

Treatment

• Bladder training

• Kegel exercises

• Drugs

Specific causes are treated, and drugs that can cause or worsen incontinence are stopped or the dosing schedule is altered (eg, a diuretic dose is timed so that a bathroom is near when the drug takes effect). Other treatment is based on type of incontinence. Regardless of type and cause, some general measures are usually helpful.

General measures: Patients may benefit from bladder training (to change voiding habits) and changes in fluid intake. Bladder training usually involves timed voiding (every 2 to 3 h) while awake. Prompted voiding is used for cognitively impaired patients; they are asked about every 2 h whether they need to

void or whether they are wet or dry. A voiding diary helps establish how often and when voiding is indicated and whether patients can sense a full bladder. Patients are instructed to limit fluid intake at certain times (eg, before going out, 3 to 4 h before bedtime), to avoid fluids that irritate the bladder (eg, caffeine-containing fluids), and to drink 48 to 64 oz (1500 to 2000 mL) of fluid a day (because concentrated urine irritates the bladder).

Pelvic muscle exercises (eg, Kegel exercises) are often effective, especially for stress incontinence. Patients must contract the pelvic muscles (pubococcygeus and paravaginal) rather than the thigh, abdominal, or buttock muscles. The muscles are contracted for 10 sec, then relaxed for 10 sec 10 to 15 times tid. Re-instruction is often necessary, and biofeedback is often useful. In women < 75 yr, cure rate is 10 to 25%, and improvement occurs in an additional 40 to 50%, especially if patients are motivated; do the exercises as instructed; and receive written instructions, follow-up visits for encouragement, or both. Pelvic floor electrical stimulation is an automated version of Kegel exercises; it uses electrical current to inhibit detrusor overactivity and contract pelvic muscles. Advantages are improved compliance and contraction of the correct pelvic muscles, but benefits over behavioral changes alone are unclear.

Some patients, especially those with restricted mobility or cognitive impairment, benefit from a portable commode. Others use absorbent pads or specialized padded undergarments. These products can greatly improve the quality of life of patients and their caregivers. However, they should not be substituted for measures that can control or eliminate incontinence, and they must be changed often to avoid skin irritation and development of UTIs.

Drugs: Drugs are often useful (see Table 230-3). Such drugs include anticholinergics and antimuscarinics, which relax the detrusor, and α-agonists, which increase sphincter tone. Drugs with strong anticholinergic effects should be used judiciously in the elderly. α-Antagonists and 5α-reductase inhibitors may be used to treat outlet obstruction in men with urge or overflow incontinence.

Urge incontinence: Treatment aims to reduce detrusor overactivity; it begins with bladder training, Kegel exercises, and relaxation techniques. Biofeedback can be used with these treatments. Drugs may also be needed, as may intermittent self-catheterization (eg, when postvoid residual volume is large). Infrequently, sacral nerve stimulation, intravesical therapies, and surgery are used.

Bladder training helps patients tolerate and ultimately inhibit detrusor contractions. Regular voiding intervals are gradually lengthened (eg, 30 min every 3 days that urinary control is maintained) to improve tolerance of detrusor contractions. Relaxation techniques can improve emotional and physical responses to the urge to void. Relaxing, standing in place or sitting down (rather than rushing to the toilet), and tightening pelvic floor muscles can help patients suppress the urge to void.

Drugs (see Table 230-3) should supplement, not replace, behavioral changes. The most commonly used are oxybutynin and tolterodine; both are anticholinergic and antimuscarinic and are available in extended-release forms that can be taken po once/day. Oxybutynin is available as a skin patch that is changed twice/wk. Newer drugs with anticholinergic and antimuscarinic properties include solifenacin and darifenacin, which are taken po once/day, and trospium, which is taken once/day or bid. Drugs may be required to suppress urgency symptoms due to DHIC. Drugs with a rapid onset of action (eg, immediate-release oxybutynin) can be used prophylactically if incontinence occurs at predictable times. Combinations of drugs may increase both efficacy and adverse effects, possibly limiting this approach in the elderly.

Sacral nerve stimulation is indicated for patients with severe urge incontinence refractory to other treatments. It is thought to work by centrally inhibiting bladder sensory afferents. The procedure begins with percutaneous nerve stimulation for at least 3 days; if patients respond, a neurostimulator is permanently implanted.

Rarely, intravesical instillation of capsaicin or resiniferatoxin (a capsaicin analog) is used when urge incontinence results from spinal cord injuries and other CNS disorders. This experimental treatment desensitizes C-fiber bladder afferents responsible for reflex bladder emptying. Injecting botulinum toxin type A into the detrusor muscle is under study as an alternative.

Surgery is a last resort, usually used only for younger patients with severe urge incontinence refractory to other treatments. Augmentation cystoplasty, in which a section of intestine is sewn into the bladder to increase bladder capacity, is most common. Intermittent self-catheterization may be required if augmentation cystoplasty results in weak bladder contractions or poor coordination of abdominal pressure (Valsalva maneuver) with sphincter relaxation. Detrusor myomectomy may be done to decrease undesired bladder contractions. As a last resort, a urinary diversion can be created to divert the urine away from the bladder. Choice of procedure is based on presence of other disorders, physical limitations, and patient preference. Neuromodulation, in which electrodes are implanted around the spinal nerve roots, is under study.

Stress incontinence: Treatment includes bladder training and Kegel exercises. Drugs, surgery, other procedures, or, in women, occlusive devices are also usually needed. Treatment is generally directed at outlet incompetence but includes treatments for urge incontinence if detrusor overactivity is present. Avoiding physical stresses that provoke incontinence can help. Losing weight may help lessen incontinence in obese patients.

Drugs (see Table 230-3) include pseudo-ephedrine, which may be useful in women with outlet incompetence; imipramine, which may be used for mixed stress and urge incontinence or for either separately; and duloxetine. If stress incontinence is due to atrophic urethritis, topical estrogen (0.3 mg conjugated or 0.5 mg estradiol once/day for 3 wk, then twice/wk after) is often effective.

Surgery and other procedures provide the best chance of cure when noninvasive treatments are ineffective. Bladder neck suspension

[**Table 230-3.** Drugs Used to Treat Incontinence]

is used to correct urethral hypermobility. Suburethral slings, injection of periurethral bulking agents, or surgical insertion of an artificial sphincter is used to treat sphincter deficiency. Choice depends on the patient's ability to tolerate surgery and need for other surgeries (eg, hysterectomy, cystocele repair) and on local experience.

Occlusive devices may be used in elderly women with or without bladder or uterine prolapse if surgical risks are high or if prior surgery for stress incontinence was ineffective. Pessaries may be effective; they elevate the bladder neck, elevate the vesicourethral junction, and increase urethral resistance by pressing the urethra against the pubic symphysis. Newer, possibly more acceptable alternatives include silicone suction caps over the urethral meatus, intraurethral occlusive devices inserted with an applicator, and intravaginal bladder neck support prostheses. Removable intraurethral plugs are under study.

Exercise regimens using vaginal cones—in which progressively heavier cones are inserted into the vagina and retained for 15 min bid by contracting pelvic floor muscles—are also under study.

Overflow incontinence: Treatment depends on whether the cause is outlet obstruction, detrusor underactivity, or both.

Outlet obstruction due to benign prostatic hyperplasia (see p. 2461) or cancer (see p. 2472) is treated with drugs or surgery; that due to urethral stricture is treated with dilation or stenting. Cystoceles in women are treated with surgery or can be reduced using a pessary (see p. 2531); unilateral suture removal or urethral adhesiolysis may be effective if cystoceles resulted from surgery. If urethral hypermobility coexists, bladder neck suspension should be done.

Detrusor underactivity requires bladder decompression (reduction of residual volume) by intermittent self-catheterization or, rarely, temporary use of an indwelling catheter. Several weeks of decompression may be required to restore bladder function. If bladder function is not fully restored, maneuvers to augment voiding (eg, double voiding, Valsalva maneuver, application of suprapubic pressure [Crede's method] during voiding) are used. A completely acontractile detrusor requires intermittent self-catheterization or use of an indwelling catheter. Using antibiotics or methenamine mandelate to prevent UTIs in patients who require intermittent self-catheterization is controversial but probably indicated if patients have

frequent symptomatic UTIs or a valvular or orthopedic prosthesis. Such prophylaxis is not helpful with indwelling catheters.

Additional treatments that may induce bladder contraction and promote emptying include electrical stimulation and the cholinergic agonist bethanechol. However, bethanechol is usually ineffective and has adverse effects (see Table 230-3).

Refractory incontinence: Absorbent pads, special undergarments, and intermittent self-catheterization may be needed. Indwelling urethral catheters are an option for patients who cannot walk to the toilet or who have urinary retention and cannot self-catheterize; these catheters are not recommended for urge incontinence because they may exacerbate detrusor contractions. If a catheter is necessary (eg, to allow healing of a pressure ulcer in patients with refractory detrusor overactivity), a narrow catheter with a small balloon should be used because it will minimize irritability; irritability can force urine out, even around a catheter. For men who can comply with treatment, condom catheters may be preferable because they reduce risk of UTIs; however, these catheters may cause skin breakdown and reduce motivation to become dry. New external collection devices may be effective in women. If involuntary bladder contractions persist, oxybutynin or tolterodine can be used. If mobility is restricted, measures to prevent skin irritation and breakdown due to urine are essential (see p. 742).

Urinary Retention

Urinary retention is incomplete emptying of the bladder or cessation of urination; it may be acute or chronic. Causes include impaired bladder contractility, bladder outlet obstruction, detrusor-sphincter dyssynergia (lack of coordination between bladder contraction and sphincter relaxation), or a combination. Retention is most common among men, in whom prostate abnormalities or urethral strictures cause outlet obstruction. In either sex, retention may be due to drugs (particularly those with anticholinergic effects, including many OTC drugs), severe fecal impaction (which increases pressure on the bladder trigone), or neurogenic bladder in patients with diabetes, multiple sclerosis, Parkinson's disease, or prior pelvic surgery resulting in bladder denervation.

Urinary retention can cause urinary frequency and urge or overflow incontinence. It may cause abdominal distention and pain. When retention develops slowly, pain may be absent. Long-standing retention predisposes to UTI and can increase bladder pressure, causing obstructive uropathy (see p. 2365).

Diagnosis

Diagnosis is obvious in patients who cannot void. In those who can void, diagnosis is by postvoid catheterization showing a residual urine volume > 100 mL. Other tests (eg, urinalysis, blood tests, ultrasonography, uro-dynamic testing, cystoscopy, cystography) are done based on clinical findings.

Treatment

• Urethral catheterization and treatment of cause

Relief of acute urinary retention requires urethral catheterization. Subsequent treatment depends on cause. In men with benign prostatic hypertrophy, drugs (usually α-adrenergic blockers or 5α-reductase inhibitors) or surgery may help decrease bladder outlet resistance. No treatment is effective for impaired bladder contractility or a neurogenic bladder; intermittent self-catheterization or indwelling catheterization is usually required. Urinary diversion is a last resort.

Neurogenic Bladder

Neurogenic bladder is bladder dysfunction (flaccid or spastic) caused by neurologic damage. The primary symptom is overflow incontinence. Risk of serious complications (eg, recurrent infection, vesicoureteral reflux, autonomic dysreflexia) is high. Diagnosis involves imaging and cystoscopy or urodynamic testing. Treatment involves catheterization or measures to trigger urination.

Any condition that impairs bladder and bladder outlet afferent and efferent signaling can cause neurogenic bladder. Causes may involve the CNS (eg, stroke, spinal injury, meningomyelocele, amyotrophic lateral sclerosis), peripheral nerves (eg, diabetic, alcoholic, or vitamin B_{12} deficiency neuropathies; herniated disks; damage due to pelvic surgery), or both (eg, Parkinson's disease, multiple sclerosis, syphilis). Bladder outlet obstruction often coexists and may exacerbate symptoms.

In **flaccid (hypotonic) neurogenic bladder**, volume is large, pressure is low, and contractions are absent. It may result from peripheral nerve damage or spinal cord damage at the S2 to S4 level. After acute cord damage, initial flaccidity may be followed by long-term flaccidity or spasticity, or bladder function may improve after days, weeks, or months.

In **spastic bladder**, volume is normal or small, and involuntary contractions occur. It usually results from brain damage or spinal cord damage above T12. Precise symptoms vary by site and severity of the lesion. Bladder contraction and external urinary sphincter relaxation are typically uncoordinated (detrusor-sphincter dyssynergia).

Mixed patterns (flaccid and spastic bladder) may be caused by many disorders, including syphilis, diabetes mellitus, brain or spinal cord tumors, stroke, ruptured intervertebral disk, and demyelinating or degenerative disorders (eg, multiple sclerosis, amyotrophic lateral sclerosis).

Symptoms and Signs

Overflow incontinence is the primary symptom in patients with a flaccid or spastic bladder. Patients retain urine and have constant overflow dribbling. Men typically also have erectile dysfunction. Patients with spastic bladder may have frequency, nocturia, and urgency or spastic paralysis with sensory deficits.

Common complications include recurrent UTIs and urinary calculi. Hydronephrosis with vesicoureteral reflux may occur because the large urine volume puts pressure on the vesicoureteral junction, causing dysfunction with reflux and, in severe cases, nephropathy. Patients with high thoracic or cervical spinal cord lesions are at risk of autonomic dysreflexia (a life-threatening syndrome of malignant hypertension, bradycardia or tachycardia, headache, piloerection, and sweating due to unregulated sympathetic hyperactivity). This disorder may be triggered by acute bladder distention (due to urinary retention) or bowel distention (due to constipation or fecal impaction).

Diagnosis

• Postvoid residual volume

• Renal ultrasonography

• Serum creatinine

• Usually cystography, cystoscopy, and cystometrography with urodynamic testing

Diagnosis is suspected clinically. Usually, postvoid residual volume is measured, renal ultrasonography is done to detect hydronephrosis, and serum creatinine is measured to assess renal function. Further studies are often not obtained in patients who are not able to self-catheterize or ask to go to the bathroom (eg, severely debilitated elderly or post-stroke patients). In patients with hydronephrosis or nephropathy who are not severely debilitated, cystography, cystoscopy, and cystometrography with urodynamic testing are usually recommended and may guide further therapy. Cystography is used to evaluate bladder capacity and detect reflux. Cystoscopy is used to evaluate duration and severity of retention (by detecting bladder trabeculations) and to check for bladder outlet obstruction. Cystometrography can determine whether bladder volume and pressure are high or low; if done during the recovery phase of flaccid bladder after spinal cord injury, it can help evaluate detrusor functional capacity and predict rehabilitation prospects (see p. 2358). Urodynamic testing of voiding flow rates with sphincter electromyography can show whether bladder contraction and sphincter relaxation are coordinated (see p. 2358).

Treatment

• Catheterization

• Increased fluid intake

• Surgery as last resort

Prognosis is good if the disorder is diagnosed and treated before kidneys are damaged.

Specific treatment involves catheterization or measures to trigger urination. General treatment includes renal function monitoring, control of UTIs, high fluid intake to decrease risk of UTIs and urinary calculi (although this measure may exacerbate incontinence), early ambulation, frequent changes of position, and dietary Ca restriction to inhibit calculus formation.

For flaccid bladder, especially if the cause is an acute spinal cord injury, immediate continuous or intermittent catheterization is needed. Intermittent self-catheterization is preferable to indwelling urethral catheterization, which has a high risk of recurrent UTIs and, in men, a high risk of urethritis, periurethritis, prostatic abscesses, and urethral fistulas. Suprapubic catheterization may be used if patients cannot self-catheterize.

For spastic bladder, treatment depends on the patient's ability to retain urine. Patients who can retain normal volumes can use techniques to trigger voiding (eg, applying suprapubic pressure, scratching the thighs); anticholinergics may be effective. For patients who cannot retain normal volumes, treatment is the same as that of urge incontinence (see p. 2358), including drugs (see Table 230-3) and sacral nerve stimulation.

Surgery is a last resort. It is usually indicated if patients have had or are at risk of severe acute or chronic sequelae or if social circumstances, spasticity, or quadriplegia prevents use of continuous or intermittent bladder drainage. Sphincterotomy (for men) converts the bladder into an open draining conduit. Sacral (S3 and S4) rhizotomy converts a spastic into a flaccid bladder. Urinary diversion may involve an ileal conduit or ureterostomy.

An artificial, mechanically controlled urinary sphincter, surgically inserted, is an option for patients who have adequate bladder capacity, good bladder emptying, and upper extremity motor skills and who can comply with instructions for use of the device; if patients do not comply, life-threatening situations (eg, renal failure, urosepsis) can result.

Interstitial Cystitis

Interstitial cystitis is noninfectious bladder inflammation that causes pain (suprapubic, pelvic, and abdominal), urinary frequency, and urgency with incontinence. Diagnosis is by history and exclusion of other disorders clinically and by cystoscopy and biopsy. With treatment, most patients improve, but cure is rare. Treatment varies but includes dietary changes, bladder training, pentosan, analgesics, and intravesical therapies.

Incidence of interstitial cystitis is unknown, but the disorder appears to be more common than once thought and may underlie other clinical syndromes (eg, chronic pelvic pain). Whites are more susceptible, and 90% of cases occur in women.

Cause is unknown, but pathophysiology may involve loss of protective urothelial mucin, with penetration of urinary K and other substances into the bladder wall, activation of sensory nerves, and smooth muscle damage. Mast cells may mediate the process, but their role is unclear.

Symptoms and Signs

Interstitial cystitis is initially asymptomatic, but symptoms appear and worsen over years as the bladder wall is damaged. Suprapubic and pelvic pressure or pain occurs, usually with urinary frequency (up to 60 times/day) or urgency. These symptoms worsen as the bladder fills and diminish when patients void; in

some people, symptoms worsen during ovulation, menstruation, seasonal allergies, physical or emotional stress, or sexual intercourse. Foods with high K content (eg, citrus fruits, chocolate, caffeinated drinks, tomatoes) may cause exacerbations. Tobacco, alcohol, and spicy foods may worsen symptoms. If the bladder wall becomes scarred, bladder compliance and capacity decrease, causing urinary urgency and frequency.

Diagnosis

• Clinical

• Cystoscopy

Diagnosis is suggested by symptoms after testing has excluded more common disorders that cause similar symptoms (eg, UTIs, pelvic inflammatory disease, chronic prostatitis or prostatodynia, diverticulitis). Cystoscopy is necessary and sometimes reveals benign bladder (Hunner's) ulcers; biopsy is required to exclude bladder cancer. Assessment of symptoms with a standardized symptom scale or during intravesical KCl infusion (K sensitivity testing) may improve diagnostic accuracy but is not yet routine practice.

Treatment

• Diet modification

• Bladder training

• Drugs (eg, pentosan, tricyclic antidepressants, NSAIDs, dimethyl sulfoxide instillation)

• Surgery as la3esort

Up to 90% of patients improve with treatment, but cure is rare. Treatment should involve avoidance of tobacco, alcohol, foods with high K content, and spicy foods as well as bladder training, drugs, intravesical therapies, and surgery as needed. Stress reduction and biofeedback (to strengthen pelvic floor muscles, eg, with Kegel exercises) may help. No treatment has been proved effective, but a combination of ≥ 2 nonsurgical treatments is recommended before surgery is considered.

The most commonly used drug is pentosan, a heparin similar to urothelial glycosaminoglycan; doses of 100 mg po tid may help restore the bladder's protective surface lining. Improvement may not be noticed for 2 to 4 mo. Intravesical instillation of 15 mL of a solution containing 100 mg of pentosan or 40,000 units of heparin plus 80 mg of lidocaine and 3 mL of Na bicarbonate may benefit patients unresponsive to oral drugs. Tricyclic antidepressants (eg, imipramine 25 to 50 mg po once/day) and NSAIDs in standard doses may relieve pain. Antihistamines (eg, hydroxyzine 10 to 50 mg once before bedtime) may help by directly inhibiting mast cells or by blocking allergic triggers.

Dimethyl sulfoxide instilled into the bladder through a catheter and retained for 15 min may deplete substance P and trigger mast cell granulation; 50 mL q 1 to 2 wk for 6 to 8 wk, repeated as needed, relieves symptoms in up to one half of patients. Intravesical instillation of BCG and hyaluronic acid are under study.

Bladder hydrodistention, cystoscopic resection of a Hunner's ulcer, and sacral nerve root (S3) stimulation help some patients.

Surgery (eg, partial cystectomy, bladder augmentation, neobladder, and urinary diversion) is a last resort for patients with intolerable pain refractory to all other treatments. Outcome is unpredictable; in some patients, symptoms persist.

Chapter 231. Obstructive Uropathy

Introduction

(Urinary Tract Obstruction)

Obstructive uropathy is structural or functional hindrance of normal urine flow, sometimes leading to renal dysfunction (obstructive nephropathy). Symptoms, less likely in chronic obstruction, are pain radiating to the T11 to T12 dermatomes, anuria, nocturia, or polyuria. Diagnosis is based on results of bladder catheterization, ultrasonography, CT, cystourethroscopy, cystourethrography, or pyelography, depending on the level of obstruction. Treatment, depending on cause, may require prompt drainage, instrumentation, surgery (eg, endoscopy, lithotripsy), hormonal therapy, or a combination of these modalities.

Each year about 2/1000 people in the US are hospitalized for obstructive uropathy. The condition has a bimodal distribution. In childhood, it is due mainly to congenital anomalies of the urinary tract. Incidence then declines until after age 60, when incidence rises, particularly in men because of the increased incidence of benign prostatic hyperplasia (BPH) and prostate cancer. Overall, obstructive uropathy is responsible for about 4% of end-stage renal disease. Hydronephrosis is found at postmortem examination in 2 to 4% of patients.

Etiology

Many conditions can cause obstructive uropathy, which may be acute or chronic, partial or complete, and unilateral or bilateral (see Table 231-1). In children, the most common causes are anatomic abnormalities (including urethral valves or stricture and stenosis at the ureterovesical or ureteropelvic junction). In young adults, the most common cause is a calculus. In older adults, the most common causes are BPH or prostate cancer, retroperitoneal or pelvic tumors, and calculi. Obstruction may occur at any level, from the renal tubules (casts, crystals) to the external urethral meatus. Proximal to the obstruction, effects may include increased intraluminal pressure, urinary stasis, UTI, or calculus formation (which may also cause obstruction). Obstruction is much more common in males, but acquired and congenital urethral strictures and meatal stenosis occur in both males

[**Table 231-1.** Causes of Obstructive Uropathy]

and females. In females, urethral obstruction may occur secondary to a tumor or as a result of stricture formation after radiation therapy, surgery, or urologic instrumentation (usually repeated dilation).

Pathophysiology

Pathologic findings consist of dilation of the collecting ducts and distal tubules and chronic tubular atrophy with little glomerular damage. Dilation takes 3 days from the onset of obstructive uropathy to develop; before then, the collecting system is relatively noncompliant and less likely to dilate. Obstructive uropathy without dilation can also occur when fibrosis or a retroperitoneal tumor encases the collecting systems, when obstructive uropathy is mild and renal function is not impaired, and in the presence of an intrarenal pelvis.

Obstructive nephropathy: Obstructive nephropathy is renal dysfunction (renal insufficiency, renal failure, or tubulointerstitial damage) resulting from urinary tract obstruction. The mechanism involves, among many factors, increased intratubular pressure, local ischemia, and, often, UTI. Obstruction may result in type 1 renal tubular acidosis due to reduced distal hydrogen secretion probably because of a defect in the hydrogen ion transporter. In this case, Na wasting can occur and predispose to ECF volume depletion. If obstruction is bilateral, nephropathy may result in renal insufficiency. Renal insufficiency may rarely occur when obstruction is unilateral because autonomic-mediated vascular or ureteral spasm may affect the functioning kidney.

Symptoms and Signs

Symptoms and signs vary with the site, degree, and rapidity of onset of obstructive uropathy.

Pain is common when obstruction acutely distends the bladder, collecting system (ie, the ureter plus the renal calyces), or renal capsule. Upper ureteral or renal pelvic lesions cause flank pain or tenderness, whereas lower ureteral obstruction causes pain that may radiate to the ipsilateral testis or labia. The distribution of kidney and ureteral pain is usually along T11 to T12. Acute complete ureteral obstruction (eg, an obstructing ureteral calculus) may cause severe pain accompanied by nausea and vomiting. A large fluid load (eg, from beer drinking or osmotic diuresis due to an IV contrast agent) causes dilation and pain if urine production increases to a level greater than the flow rate through the area of obstruction. Pain is typically minimal or absent with partial or slowly developing obstructive uropathy (eg, congenital ureteropelvic junction obstruction, pelvic tumor). Hydronephrosis may occasionally produce a palpable flank mass, particularly in massive hydronephrosis of infancy and childhood.

Urine volume does not diminish in unilateral obstruction unless it occurs in the only functioning kidney. Absolute anuria occurs with complete obstruction at the level of the bladder or urethra. Partial obstruction at that level may cause difficulty voiding or abnormalities of the urine stream. In partial obstruction, urine output is often normal and is rarely increased. Increased urine output with polyuria and nocturia occur if the ensuing nephropathy causes impaired renal concentrating capacity and Na reabsorption. Long-standing nephropathy may also result in hypertension.

Infection complicating obstruction may cause dysuria, pyuria, urinary urgency and frequency, referred kidney and ureteral pain, costovertebral angle tenderness, fever, and, occasionally, septicemia.

Diagnosis

- Urinalysis and serum electrolytes, BUN, and creatinine
- Bladder catheterization, sometimes followed by cystourethroscopy and voiding cystourethrography for suspected urethral obstruction
- Imaging for suspected ureteral or more proximal obstruction or for hydronephrosis without apparent obstruction

Obstructive uropathy should be considered in patients with any of the following:

- Diminished or absent urine output
- Unexplained renal insufficiency
- Pain that suggests distention in the urinary tract
- A pattern of oliguria or anuria alternating with polyuria

The history may suggest symptoms of BPH, prior cancer, or urolithiasis. Because early relief of obstruction usually achieves the best outcome, diagnosis should be as rapid as possible.

Urinalysis and serum chemistries (serum electrolytes, BUN, creatinine) should be obtained. Other tests are done depending on symptoms and suspected level of obstruction. Infection with urinary obstruction requires immediate evaluation and treatment.

In an asymptomatic patient with longstanding obstructive uropathy, urinalysis may be normal or reveal only a few casts, WBCs, or RBCs. In a patient with acute renal failure who has a normal urinalysis, bilateral obstructive nephropathy should be considered.

If serum chemistries indicate renal insufficiency, obstruction is probably bilateral and severe or complete. Other findings in bilateral obstruction with nephropathy may include hyperkalemia. Hyperkalemia may result from type 1 renal tubular acidosis due to decreased hydrogen ion and K secretion by distal

segments of the nephron.

Evaluation of suspected urethral obstruction: If urine output is diminished or if there is a distended bladder or suprapubic pain, bladder catheterization should be done. If catheterization results in a normal flow of urine or if the catheter is difficult to pass, a urethral obstruction (eg, prostatic enlargement, stricture, or valve) is suspected. Patients with such findings should have cystourethroscopy along with voiding cystourethrography.

Voiding cystourethrography shows nearly all bladder neck and urethral obstructions as well as vesicoureteral reflux, adequately displaying the anatomy and the volume of urine left in the bladder after voiding (postvoiding residual volume).

If symptoms of urethral obstruction are absent or if cystourethroscopy and voiding cystourethrography show no obstruction, the site of obstruction is presumed to be at the ureters or proximal to them.

Evaluation of ureteral or more proximal obstruction: Patients undergo imaging tests to detect the presence and site of obstruction. The choice and sequencing of tests depend on the clinical scenario.

Abdominal ultrasonography is the initial imaging test of choice in most patients without urethral abnormalities because it avoids potential allergic and toxic complications of contrast agents and allows assessment of associated renal parenchymal atrophy. Ultrasonography is aimed at detection of hydronephrosis. However, the false-positive rate is 25% if only minimal criteria (visualization of the collecting systems) are considered in the diagnosis. Also, absence of hydronephrosis (and false-negative results) can occur if obstruction is early (in the first few days) or mild or if retroperitoneal fibrosis or tumor encases the collecting system, preventing dilation of the ureter.

CT is sensitive for diagnosing obstructive nephropathy and is used when obstruction cannot be shown by ultrasonography or by intravenous urography. Unenhanced helical CT is the modality of choice. It is particularly accurate for obstruction due to ureteral calculi. The combination of ultrasonography, plain abdominal x-ray, and, if necessary, CT reveals obstructive uropathy in > 90% of patients, but ultrasonography and CT may not be able to differentiate hydronephrosis from multiple renal or parapelvic cysts.

Duplex Doppler ultrasonography can usually show unilateral obstructive uropathy in the first few days of acute obstruction before the collecting system dilates by detecting an increased resistive index (a reflection of increased renal vascular resistance) in the affected kidney. This modality is less useful in obesity and in bilateral obstruction, which cannot be distinguished from intrinsic renal disease.

IVU (contrast urography, intravenous pyelography [IVP], excretory urography) has been largely superseded by CT and MRI (with or without contrast). However, when CT cannot identify the level of obstructive uropathy and when acute obstructive uropathy is thought to be caused by calculi, sloughed papilla, or a blood clot, IVU or retrograde pyelography may be indicated.

Antegrade or retrograde pyelography is preferred to studies that involve vascular administration of contrast agents in the azotemic patient. Retrograde studies are done through a cystoscope, whereas antegrade studies require placement of a catheter percutaneously into the renal pelvis. Patients with intermittent obstruction should be studied when they are having symptoms; otherwise, the obstruction may be missed.

Radionuclide scans also require some renal function but can detect obstruction without the use of contrast agents. When a kidney is assessed as nonfunctioning, a radionuclide scan can determine perfusion and identify functional renal parenchyma. Because this test cannot detect specific areas of obstruction, it is mainly used in conjunction with diuresis renography to evaluate hydronephrosis without apparent obstruction.

MRI can be used when avoiding ionizing radiation is important (eg, in young children or pregnant women). However, it is not superior in accuracy to ultrasonography or CT.

Evaluation of hydronephrosis without apparent obstruction: Testing may be necessary to determine whether back or flank pain is caused by obstruction in patients who have hydronephrosis but no obvious obstruction revealed by other imaging tests. Testing may also be done to detect otherwise unrecognized obstruction in patients with incidentally recognized hydronephrosis.

In **diuresis renography**, a loop diuretic (eg, furosemide 0.5 mg/kg IV) is given before a radionuclide renal scan (or an IVU). The patient must have sufficient renal function to respond to the diuretic. If obstruction is present, the rate of washout of the radionuclide (or contrast agent) from the time the tracer appears in the renal pelvis is reduced to a half-life of > 20 min (normal is < 15 min). If the renogram is negative or equivocal but the patient is symptomatic, a perfusion pressure flow study is done via percutaneous insertion of a catheter into the dilated renal pelvis, followed by fluid perfusion into the pelvis at 10 mL/min. The patient is in a prone position. If obstructive uropathy is present, in spite of the marked increase in urine flow, the rate of washout of the radionuclide during renal scanning is delayed, and there will be further dilation of the collecting system on IVU and elevation of the renal pelvic pressure to > 22 mm Hg during perfusion. A renogram or perfusion study that causes pain similar to the patient's initial complaint is interpreted as positive. If the perfusion study is negative, the pain probably has a nonrenal cause. False-positive and false-negative results are common for both tests.

Prognosis

Most obstruction can be corrected, but a delay in therapy can lead to irreversible renal damage. How long it takes for nephropathy to develop and how reversible nephropathy is vary depending on the underlying pathology, the presence or absence of UTI, and the degree and duration of the obstruction. In general, acute renal failure due to a ureteral calculus is reversible, with adequate return of renal function. With chronic progressive obstructive uropathy, renal dysfunction may be partially or completely irreversible. Prognosis is worse if UTI remains untreated.

Treatment

• Relief of obstruction

Treatment consists of eliminating the obstruction by surgery, instrumentation (eg, endoscopy, lithotripsy), or drug therapy (eg, hormonal therapy for prostate cancer). Prompt drainage in hydronephrosis is indicated if renal function is compromised, UTI persists, or pain is uncontrollable or persistent. Lower obstructive uropathy may require catheter or more proximal drainage. Indwelling pigtail ureteral catheters can be placed for acute or long-term drainage in selected patients. Temporary drainage using a percutaneous technique may be needed in severe obstructive uropathy, UTI, or calculi. Intensive treatment for UTI and renal failure is imperative.

In the case of hydronephrosis without evident obstruction, surgery should be considered if the patient has pain and a positive diuretic renogram. However, no therapy is necessary in an asymptomatic patient with a negative diuretic renogram or with a positive diuretic renogram but normal renal function.

Chapter 232. Urinary Calculi

Introduction

(Nephrolithiasis; Stones; Urolithiasis)

Urinary calculi are solid particles in the urinary system. They may cause pain, nausea, vomiting, hematuria, and, possibly, chills and fever from secondary infection. Diagnosis is based on urinalysis and radiologic imaging, usually noncontrast helical CT. Treatment is with analgesics, antibiotics for infection, and, sometimes, extracorporeal shock wave lithotripsy or endoscopic procedures.

About 1/1000 adults in the US is hospitalized annually because of urinary calculi, which are also found in about 1% of all autopsies. Up to 12% of men and 5% of women will develop a urinary calculus by age 70. Calculi vary from microscopic crystalline foci to calculi several centimeters in diameter. A large calculus, called a staghorn calculus, can fill an entire renal calyceal system.

Etiology

About 85% of calculi in the US are composed of Ca, mainly Ca oxalate (see Table 232-1); 10% are uric acid; 2% are cystine; and the remainder are Mg ammonium phosphate (struvite).

General risk factors include disorders that increase urinary salt concentration, either by increased excretion of Ca or uric acid salts, or by decreased excretion of urine or citrate.

For **Ca calculi,** risk factors vary by population. The main risk factor in the US is hypercalciuria, a hereditary condition present in 50% of men and 75% of women with Ca calculi; thus, patients with a family history of calculi are at increased risk of recurrent calculi. These patients have normal serum Ca but elevated urinary Ca: > 250 mg/day (> 6.2 mmol/day) in men and > 200 mg/day (> 5.0 mmol/day) in women. Hypocitruria (urinary citrate < 350 mg/day [1820 µmol/day]), present in about 40 to 50% of Ca calculi-formers, promotes Ca calculi formation because citrate normally binds urinary Ca and inhibits the crystallization of Ca salts. About 5 to 8% of calculi are caused by renal tubular acidosis. About 1 to 2% of patients with Ca calculi have primary hyperparathyroidism. Rare causes are sarcoidosis, vitamin D intoxication, hyperthyroidism, multiple myeloma, metastatic cancer, and hyperoxaluria. Hyperoxaluria (urinary oxalate > 40 mg/day [> 440 µmol/day]) can be primary or caused by excess ingestion of oxalate-containing foods (eg, rhubarb, spinach, cocoa, nuts, pepper, tea) or by excess oxalate absorption due to various enteric diseases (eg, bacterial overgrowth syndromes, chronic pancreatic or biliary disease) or ileojejunal surgery. Other risk factors include taking high doses of vitamin C, a Ca-restricted diet (possibly because dietary Ca binds dietary oxalate), and mild hyperuricosuria. Mild hyperuricosuria, defined as urinary uric acid > 800 mg/day (> 5 mmol/day) in men or > 750 mg/day (> 4 mmol/day) in women, is almost always caused by excess intake of purine (in proteins, usually from meat, fish, and poultry); it may cause Ca oxalate calculus formation (hyperuricosuric Ca oxalate nephrolithiasis).

Uric acid calculi develop with increased urine acidity (urine pH < 5.5), or rarely with severe hyperuricosuria (urinary uric acid > 1500 mg/day [> 9 mmol/day]), which crystallizes undissociated uric acid. Uric acid crystals may comprise the entire calculus or, more commonly, provide a nidus on which Ca or mixed Ca and uric acid calculi can form.

Cystine calculi occur only in the presence of cystinuria (see p. 2990).

Mg ammonium phosphate calculi (struvite, infection calculi) indicate the presence of a UTI caused by urea-splitting bacteria (eg, *Proteus* sp, *Klebsiella* sp). The calculi must be treated as infected foreign bodies and

[**Table 232-1.** Composition of Urinary Calculi]

removed in their entirety. Unlike other types of calculi, Mg ammonium phosphate calculi occur 3 times

more frequently in women.

Pathophysiology

Urinary calculi may remain within the renal parenchyma or renal pelvis or be passed into the ureter and bladder. During passage, calculi irritate the ureter and may become lodged, obstructing urine flow and causing hydroureter and sometimes hydronephrosis. Common areas of lodgment include the ureteropelvic junction, the distal ureter (at the level of the iliac vessels), and the ureterovesical junction. Typically, a calculus must have a diameter > 5 mm to become lodged. Calculi ≤ 5 mm are likely to pass spontaneously.

Even partial obstruction causes decreased glomerular filtration, which may persist briefly after the calculus has passed. With hydronephrosis and elevated glomerular pressure, renal blood flow declines, further worsening renal function. Generally, however, permanent renal dysfunction occurs only after about 28 days of complete obstruction.

Secondary infection can occur with longstanding obstruction, but most patients with Ca-containing calculi do not have infected urine.

Symptoms and Signs

Even large calculi remaining in the renal parenchyma or renal pelvis are usually asymptomatic unless they cause obstruction. Symptoms, such as severe pain, often accompanied by nausea and vomiting, and sometimes gross hematuria, usually occur when calculi pass into the ureter, cause obstruction, or both. Pain (renal colic) is of variable intensity but is typically excruciating and intermittent, often occurs cyclically, and lasts 20 to 60 min. Nausea and vomiting are common. Pain in the flank or kidney area that radiates across the abdomen suggests upper ureteral or renal pelvic obstruction. Pain that radiates along the course of the ureter into the genital region suggests lower ureteral obstruction. Suprapubic pain along with urinary urgency and frequency suggests a distal ureteral, ureterovesical, or bladder calculus.

On examination, patients may be in obvious extreme discomfort, often ashen and diaphoretic. Patients with renal colic may be unable to lie still and may pace, writhe, or constantly shift position. The abdomen may be somewhat tender on the affected side as palpation increases pressure in the already-distended ureter, but peritoneal signs (guarding, rebound, rigidity) are lacking. For some patients, the first symptom is hematuria or either gravel or a calculus in the urine. Other patients may have symptoms of a UTI, such as fever, dysuria, or cloudy or foul-smelling urine.

Diagnosis

• Clinical differential diagnosis

• Urinalysis

• Imaging

• Determination of calculus composition

The symptoms and signs suggest the diagnosis. With peritonitis (eg, due to appendicitis, ectopic pregnancy, or pelvic inflammatory disease), pain is usually constant, and patients lie still because movement worsens pain. Patients often have rebound tenderness or rigidity. Cholecystitis may cause colicky pain, usually in the epigastrium or right upper quadrant, often with Murphy's sign. Bowel obstruction may cause colicky abdominal pain and vomiting, but the pain is usually bilateral and not located primarily in the flank or along the ureter. Pancreatitis may cause upper abdominal pain and vomiting, but the pain is usually constant, may be bilateral, and is usually not along the flank or ureter. With most of these disorders, urinary symptoms are uncommon and other symptoms may suggest which organ system is actually involved (eg, vaginal discharge or bleeding in pelvic disorders among females). Dissecting aortic aneurysm must be considered, particularly in the elderly, because, if a renal artery is affected, it can cause hematuria, pain that radiates along a ureteral distribution, or both. Other

considerations in the general evaluation of acute abdominal pain are discussed elsewhere (see p. 106).

Patients suspected of having a calculus causing colic require urinalysis and usually an imaging study. If calculus is confirmed, evaluation of the underlying disorder, including calculus composition testing, is required.

Urinalysis: Macroscopic or microscopic hematuria is common, but urine may be normal despite multiple calculi. Pyuria with or without bacteria may be present. Pyuria suggests infection, particularly if combined with suggestive clinical findings, such as foul-smelling urine or a fever. A calculus and various crystalline substances may be present in the sediment. If so, further testing is usually necessary because the composition of the calculus and crystals cannot be determined conclusively by microscopy. The only exception is when typical hexagonal crystals of cystine are found in a concentrated, acidified specimen, confirming cystinuria.

Imaging tests: Noncontrast helical CT should be done. This study can detect the location of a calculus as well as the degree of obstruction. Moreover, helical CT may also reveal another cause of the pain (eg, aortic aneurysm). For patients who have recurrent calculi, cumulative radiation exposure from multiple CT scans is a concern. For patients with typical symptoms, ultrasonography or plain abdominal x-rays can usually confirm presence of a calculus with minimal or no radiation exposure.

Although most urinary calculi are demonstrable on plain x-ray, neither their presence nor their absence obviates the need for more definitive imaging, so this study can be avoided. Both renal ultrasonography and intravenous urography (IVU) can identify calculi and hydronephrosis, but ultrasonography is less sensitive for small calculi in patients without hydronephrosis, and IVU is time consuming and exposes the patient to the risk of IV contrast agents; these studies are generally used if helical CT is unavailable.

Identifying the cause: The calculus is obtained by straining the urine (or, if necessary, during operative removal) and sent to the laboratory for crystallography. Some calculi are brought in by patients. Urine specimens that show microscopic crystals can also be sent for crystallography. Patients with a single Ca calculus without additional risk factors for calculi require only urinalysis and plasma Ca concentration on 2 occasions to exclude hyperparathyroidism. Predisposing factors, such as a high-protein diet or vitamin C or D supplements, should be sought. Patients with a strong family history of calculi, conditions that might predispose to calculi formation (eg, sarcoidosis, bone metastases, multiple myeloma), or conditions that would make it difficult to treat calculi (eg, solitary kidney, urinary tract anomalies) require evaluation for all possible causative disorders and risk factors. This evaluation should include serum electrolytes, uric acid, and Ca on 2 separate occasions. Follow-up determination of parathyroid hormone levels is done if necessary. Urine tests should include routine urinalysis and 2 separate 24-h urine collections for urine volume, pH, and excretion of Ca, uric acid, citrate, oxalate, Na, and creatinine.

Treatment

- Analgesia
- Facilitate calculus passage (eg, with α-receptor blockers or Ca channel blockers)
- For persistent or infection-causing calculi, removal using extracorporeal shock wave lithotripsy or endoscopic techniques

Analgesia: Renal colic may be relieved with opioids, such as morphine and, for a rapid onset, fentanyl. Ketorolac 30 mg IV is rapidly effective and nonsedating. Vomiting usually resolves as pain decreases, but persistent vomiting can be treated with an antiemetic (eg, ondansetron 10 mg IV).

Facilitating calculus passage: Although increasing fluids (either oral or IV) has traditionally been recommended, it has not been proved to speed the passage of calculi. Patients with calculi with a diameter of < 1 cm who have no infection or obstruction, whose pain is controlled with analgesics, and who can tolerate liquids can be treated at home with analgesics and with α-receptor blockers (eg, tamsulosin 0.4 mg po once/day) or Ca channel blockers to facilitate calculus passage. Calculi that have not passed within 6 wk typically require removal. In patients with infection and obstruction, calculi should

be removed as soon as possible.

Calculus removal: The technique used for removal depends on the location and size of the calculi. Techniques include extracorporeal shock wave lithotripsy and endoscopic techniques. Endoscopic techniques may involve rigid or flexible scopes and may involve direct-vision removal (basketing), fragmentation with some sort of lithotripsy (eg, pneumatic, electrohydraulic, laser), or both. For symptomatic calculi < 1 cm in diameter in the renal pelvis or proximal ureter, extracorporeal shock wave lithotripsy is a reasonable first option for therapy. For larger calculi or if lithotripsy is unsuccessful, ureteroscopy (done in a retrograde fashion) with holmium laser lithotripsy is usually used. Sometimes removal is possible using an endoscope inserted anterograde through the kidney. For midureteral calculi, ureteroscopy with holmium laser lithotripsy is usually the treatment of choice. Shock wave lithotripsy is an alternative. For distal ureteral calculi, endoscopic techniques, such as direct removal and use of lithotripsy (eg, pneumatic, electro-hydraulic, laser), are considered by many to be the procedures of choice. Shock wave lithotripsy can also be used.

Calculus dissolution: Uric acid calculi in the upper or lower urinary tract occasionally may be dissolved by prolonged alkalinization of the urine with K citrate 20 mEq po bid to tid, but chemical dissolution of other calculi is not possible.

Prevention

In a patient who has passed a first Ca calculus, the likelihood of forming a 2nd calculus is about 15% at 1 yr, 40% at 5 yr, and 80% at 10 yr. Recovery and analysis of the calculus, measurement of calculus-forming substances in the urine, and the clinical history are needed to plan prophylaxis. In < 3% of patients, no metabolic abnormality is found. These patients seemingly cannot tolerate normal amounts of calculus-forming salts in their urine without crystallization. Thiazide diuretics, K citrate, and increased fluid intake may reduce their calculus production rate.

For **hypercalciuria,** patients may receive thiazide diuretics (eg, chlorthalidone 25 mg po once/day or indapamide 1.25 mg po once/day) to lower urine Ca excretion and thus prevent urinary supersaturation with Ca oxalate. Patients are encouraged to increase their fluid intake to ≥ 3 L/day. A diet that is low in Na and high in K is recommended. Restriction of dietary animal protein is also recommended.

For patients with **hypocitruria,** K citrate (20 mEq bid) enhances citrate excretion. A normal Ca intake is recommended, and Ca restriction is avoided. Oral orthophosphate has not been thoroughly studied.

Hyperoxaluria prevention varies. Patients with small-bowel disease can be treated with a combination of high fluid intake, Ca loading (usually in the form of Ca citrate 400 mg po bid), cholestyramine, and a low-oxalate, low-fat diet. Hyperoxaluria may respond to pyridoxine 5 to 500 mg po once/day, possibly by increasing transaminase activity, because this activity is responsible for the conversion of glyoxylate, the immediate oxalate precursor, to glycine.

In **hyperuricosuria,** intake of meat, fish, and poultry should be reduced. If the diet cannot be changed, allopurinol 300 mg each morning lowers uric acid production. For uric acid calculi, the urine pH must be increased to between 6 and 6.5 by giving an oral alkalinizing drug that contains K (eg, K citrate 20 mEq bid) along with increased fluid intake.

Infection with **urea-splitting bacteria** requires culture-specific antibiotics and complete removal of all calculi. If eradication of infection is impossible, long-term suppressive therapy (eg, with nitrofurantoin) may be necessary. In addition, acetohydroxamic acid can be used to reduce the recurrence of struvite calculi.

To prevent recurrent **cystine calculi,** urinary cystine levels must be reduced to < 250 mg cystine/L of urine. Any combination of increasing urine volume along with reducing cystine excretion (eg. with α-mercaptopropionylglycine or penicillamine) should reduce the urinary cystine concentration.

Chapter 233. Urinary Tract Infections

Introduction

Urinary tract infections (UTIs) can be divided into upper tract infections, which involve the kidneys, and lower tract infections, which involve the bladder, urethra, or prostate. However, in practice, and particularly in children, differentiating between the sites may be difficult or impossible. Moreover, infection often moves from one area to the other.

Most UTIs are caused by enteric bacteria. The remainder are due to sexually transmitted pathogens (see p. 1466), mycobacteria (see p. 1302), fungi (see pp. 1318 and 2380), viruses, and parasites. The predominant parasitic causes of UTIs are filariasis, trichomoniasis, leishmaniasis, malaria, and schistosomiasis. These parasitic diseases are discussed in other chapters of THE MANUAL. Of the parasitic diseases, only trichomoniasis is common in the US. Adenoviruses are implicated in hemorrhagic cystitis.

Bacterial Urinary Tract Infections

(See also Ch. 135 and Prostatitis on p. 2462.)

Bacterial UTIs can involve the urethra, prostate, bladder, or kidneys. Symptoms may be absent or include urinary frequency and urgency, dysuria, lower abdominal pain, and flank pain. Systemic symptoms and even sepsis may occur with kidney infection. Diagnosis is based on analysis and culture of urine. Treatment is with antibiotics.

Among adults aged 20 to 50 yr, UTIs are about 50-fold more common in women. The incidence increases in patients > 50 yr, but the female:male ratio decreases because of the increasing frequency of prostate disease.

Pathophysiology

The urinary tract, from the kidneys to the urethral meatus, is normally sterile and resistant to bacterial colonization despite frequent contamination of the distal urethra with colonic bacteria. Mechanisms that maintain the tract's sterility include urine acidity, emptying of the bladder at micturition, ureterovesical and urethral sphincters, and various immunologic and mucosal barriers.

About 95% of UTIs occur when bacteria ascend the urethra to the bladder and, in the case of acute uncomplicated pyelonephritis, ascend the ureter to the kidney. The remainder of UTIs are hematogenous. Systemic infection can result from UTI, particularly in the elderly. About 6.5% of cases of hospital-acquired bacteremia are attributable to UTI.

Complicated UTI is considered to be present when there are underlying factors that predispose to ascending bacterial infection. Predisposing factors include urinary instrumentation (eg, catheterization, cystoscopy), anatomic abnormalities, and obstruction of urine flow or poor bladder emptying. A common consequence of anatomic abnormality is vesicoureteral reflux (VUR), which is present in 30 to 45% of young children with symptomatic UTI (see p. 2844). VUR is usually caused by a congenital defect that results in incompetence of the ureterovesical valve. It is most often due to a short intramural segment (the ureter normally transits the bladder wall at an angle; the resultant lengthy segment is more readily closed by muscular contraction than the shorter segment that occurs when the ureter passes straight through the wall). VUR can also be acquired in patients with a flaccid bladder due to spinal cord injury. Other anatomic abnormalities predisposing to UTI include urethral valves (a congenital obstructive abnormality), delayed bladder neck maturation, bladder diverticulum, and urethral duplications. Urine flow can be compromised by calculi and tumors. Bladder emptying can be impaired by neurogenic dysfunction (see p. 2363), pregnancy, uterine prolapse, cystocele, and prostatic enlargement. UTI caused by congenital factors presents most commonly in childhood. Most other factors are more common in the elderly.

Uncomplicated UTI occurs without underlying abnormality or impairment of urine flow. It is most common in young women but also somewhat common in younger men who have unprotected anal intercourse, an

uncircumcised penis, unprotected intercourse with a woman whose vagina is colonized with urinary pathogens, or AIDS. Risk factors in women include sexual intercourse, diaphragm and spermicide use, antibiotic use, and a history of recurrent UTIs. Even use of spermicide-coated condoms increases risk of UTI in women. The increased risk of UTI in women using antibiotics or spermicides probably occurs because of alterations in vaginal flora that allow overgrowth of *Escherichia coli*. In elderly women, soiling of the perineum due to fecal incontinence increases risk. Patients of both sexes with diabetes have an increased incidence and severity of infections.

Etiology

Commensal colonic gram-negative aerobic bacteria cause most bacterial UTIs. In relatively normal tracts, strains of *E. coli* with specific attachment factors for transitional epithelium of the bladder and ureters are the most frequent causes. The remaining gram-negative urinary pathogens are other enterobacteria, especially *Klebsiella, Proteus mirabilis*, and *Pseudomonas aeruginosa*. Enterococci (group D streptococci) and coagulase-negative staphylococci (eg, *Staphylococcus saprophyticus)* are the most frequently implicated gram-positive organisms.

E. coli causes > 75% of community-acquired UTIs in all age groups; *S. saprophyticus* accounts for about 10%. In hospitalized patients, *E. coli* accounts for about 50% of cases. The gram-negative species *Klebsiella, Proteus*, *Enterobacter*, and *Serratia* account for about 40%, and the gram-positive bacterial cocci *Enterococcus faecalis* and *S. saprophyticus* and *S. aureus* account for the remainder.

Classification

Urethritis: Infection of the urethra with bacteria (or with protozoa, viruses, or fungi) occurs when organisms that gain access to it acutely or chronically colonize the numerous periurethral glands in the bulbous and pendulous portions of the male urethra and in the entire female urethra. The sexually transmitted pathogens *Chlamydia trachomatis* (see p. 1468), *Neisseria gonorrhoeae* (see p. 1471), *Trichomonas vaginalis* (see p. 1481), and herpes simplex virus (see p. 1417) are common causes in both sexes.

Cystitis: In women, sexual intercourse usually precedes uncomplicated cystitis (honeymoon cystitis). In men, bacterial infection of the bladder is usually complicated and generally results from ascending infection from the urethra or prostate or is secondary to urethral instrumentation. The most common cause of recurrent cystitis in men is chronic bacterial prostatitis.

Acute urethral syndrome: Acute urethral syndrome, which occurs in women, causes dysuria and pyuria (dysuria-pyuria syndrome) due to bacterial urinary pathogens. Occasionally, it is caused by *N. gonorrhoeae*, TB, or fungal disease or by trauma or inflammation of the urethra. Patients with acute urethral syndrome have dysuria, frequency, and pyuria, but urine cultures are either negative or show colony counts that are < 10^5/mL, which is less than the traditional criterion for bacterial UTI.

Asymptomatic bacteruria: Certain patients, primarily elderly women and patients with diabetes or those who require long-term use of indwelling catheters, have persistent bacteriuria with changing flora that is both asymptomatic and refractory to treatment. WBC count in urine may be modestly elevated. Most of these patients are best left untreated because the usual result of treatment is the establishment of highly resistant organisms. Asymptomatic bacteriuria can also occur in pregnant women and may cause infection of the urinary tract, sepsis, low birth weight, spontaneous abortion, premature delivery (see p. 2650), and stillbirth, so treatment is indicated.

Acute pyelonephritis: Pyelonephritis is bacterial infection of the kidney parenchyma. The term should not be used to describe tubulointerstitial nephropathy unless infection is documented. In women, about 20% of community-acquired bacteremias are due to pyelonephritis. Pyelonephritis is uncommon in men with a normal urinary tract.

Although obstruction (eg, strictures, calculi, tumors, neurogenic bladder, VUR) predis-poses to pyelonephritis, most women with pyelonephritis have no demonstrable functional or anatomic defects.

Cystitis alone or anatomic defects may cause reflux. This tendency is greatly enhanced when ureteral peristalsis is inhibited (eg, during pregnancy, by obstruction, by endotoxins of gram-negative bacteria). Pyelonephritis or focal abscess may be due to hematogenous spread, which is infrequent and usually results from bacteremia with virulent bacilli (eg, *Salmonella* sp, *S. aureus*). Pyelonephritis is common in young girls and in pregnant women after instrumentation or bladder catheterization.

The kidney usually is enlarged because of inflammatory PMNs and edema. Infection is focal and patchy, beginning in the pelvis and medulla and extending into the cortex as an enlarging wedge. Chronic inflammatory cells appear within a few days, and medullary and subcortical abscesses may develop. Normal parenchymal tissue between foci of infection is common. Papillary necrosis may be evident in acute pyelonephritis associated with diabetes, obstruction, sickle cell disease, pyelonephritis in renal transplants, pyelonephritis due to candidiasis, or analgesic nephropathy. Although acute pyelonephritis is frequently associated with renal scarring in children, similar scarring in adults is not detectable in the absence of reflux or obstruction.

Symptoms and Signs

In the elderly, UTIs are often asymptomatic. Elderly patients, and those with a neurogenic bladder or an indwelling catheter, may present with sepsis and delirium but without symptoms referable to the urinary tract.

When symptoms are present, they may not correlate with the location of the infection within the urinary tract because there is considerable overlap; however, some generalizations are useful.

In **urethritis,** the main symptoms are dysuria and, primarily in males, urethral discharge. Discharge tends to be purulent when due to *N. gonorrhoeae* and whitish and mucoid when not.

Cystitis onset is usually sudden, typically with frequency, urgency, and burning or painful voiding of small volumes of urine. Nocturia, with suprapubic and often low back pain, is common. The urine is often turbid, and gross hematuria occurs in about 30% of patients. A low-grade fever may develop. Pneumaturia (passage of air in the urine) can occur when infection results from a vesicoenteric or vesicovaginal fistula or from emphysematous cystitis.

In **acute pyelonephritis,** symptoms may be the same as those of cystitis; one third of patients have frequency and dysuria. However, with pyelonephritis, symptoms typically include chills, fever, flank pain, colicky abdominal pain, nausea, and vomiting. If abdominal rigidity is absent or slight, a tender, enlarged kidney is sometimes palpable. Costovertebral angle percussion tenderness is generally present on the infected side. In children, symptoms often are meager and less characteristic (see p. 2845).

Diagnosis

• Urinalysis

• Sometimes urine culture

Diagnosis by culture is not always necessary. If done, diagnosis by culture requires demonstration of significant bacteriuria in properly collected urine.

Urine collection: If a sexually transmitted disease (STD) is suspected, a urethral swab for STD testing is obtained prior to voiding. Urine collection is then by clean-catch or catheterization.

To obtain a **clean-catch, midstream-voided specimen,** the urethral opening is washed with a mild, nonfoaming disinfectant and air dried. Contact of the urinary stream with the mucosa should be minimized by spreading the labia in women and by pulling back the foreskin in uncircumcised men. The first 5 mL of urine is not captured; the next 5 to 10 mL is collected in a sterile container.

A **specimen obtained by catheterization** is preferable in older women (who typically have difficulty

obtaining a clean-catch specimen) and in women with vaginal bleeding or discharge. Many clinicians also use catheterization to obtain a specimen if evaluation includes a pelvic examination. Diagnosis in patients with indwelling catheters is discussed elsewhere (see p. 2378).

Urine testing: Microscopic examination of urine is useful but not definitive. Pyuria is defined as ≥ 8 WBCs/μL of uncentrifuged urine, which corresponds to 2 to 5 WBCs/high-power field in spun sediment. Most truly infected patients have > 10 WBCs/μL. The presence of bacteria in the absence of pyuria, especially when several strains are found, is usually due to contamination during sampling. Microscopic hematuria occurs in up to 50% of patients, but gross hematuria is uncommon. WBC casts, which require special stains to differentiate from renal tubular casts, indicate only an inflammatory reaction; they can be present in pyelonephritis, glomerulonephritis, and noninfective tubulointerstitial nephritis.

Dipstick tests also are commonly used. A positive nitrite test on a freshly voided specimen (bacterial replication in the container renders results unreliable if the specimen is not tested rapidly) is highly specific for UTI, but the test is not very sensitive. The leukocyte esterase test is very specific for the presence of > 10 WBCs/μL and is fairly sensitive. In adult women with uncomplicated UTI with typical symptoms, most clinicians consider positive microscopic and dipstick tests sufficient; in these cases, given the likely pathogens, cultures are unlikely to change treatment but add significant expense.

Cultures are recommended when symptoms are suggestive but urinalysis is nondiagnostic; for complicated UTI, including UTI in patients with diabetes, immunosuppression, recent hospitalization or urethral instrumentation, or recurrent UTI; for patients > 65 yr; and perhaps for patients with symptoms of pyelonephritis. All prepubertal children should have a urine culture when a UTI is suspected. Urine should be cultured as soon as possible or stored at 4° C if a delay of > 10 min is expected. Samples contaminated with large numbers of epithelial cells are unlikely to be helpful. An uncontaminated specimen should be obtained for culture. Criteria, based on the guidelines of the Infectious Diseases Society of America, for bacteriuria are:

- Among women with suspected asymptomatic bacteriuria, 2 consecutive clean-catch voided specimens from which the same bacterial strain is isolated in colony counts of > 10^5/mL
- Among women with suspected acute urethral syndrome, a clean-catch voided specimen from which a single bacterial species is isolated in colony counts from 10^2 to 10^4/mL
- Among men, a clean-catch voided specimen from which a single bacterial species is isolated in colony counts > 10^5/mL
- Among women or men, a catheter-obtained specimen from which a single bacterial species is isolated in colony counts of > 10^2/mL

Occasionally, UTI is present despite lower colony counts, possibly because of prior antibiotic therapy, very dilute urine (sp gr < 1.003), or obstruction to the flow of grossly infected urine. Repeating the culture improves the diagnostic accuracy of a positive result, ie, may differentiate between a contaminant and a true positive result.

Infection localization: Clinical differentiation between upper and lower UTI is impossible in many patients, and testing is not usually advisable. When the patient has high fever, costovertebral angle tenderness, and gross pyuria with casts, pyelonephritis is highly likely. The best noninvasive technique for differentiating bladder from kidney infection appears to be the response to a short course of antibiotic therapy. If the urine has not cleared after 3 days of treatment, pyelonephritis should be sought.

Symptoms similar to those of cystitis and urethritis can occur with vaginitis, which may cause dysuria from the passage of urine across inflamed labia. Vaginitis can often be distinguished by the presence of vaginal discharge, vaginal odor, and dyspareunia.

Other testing: Seriously ill patients require evaluation for sepsis, typically with CBC, electrolytes, BUN, creatinine, and blood cultures. Patients with abdominal pain or tenderness are evaluated for other causes

of an acute abdomen (see p. 106). Pyuria without bacteriuria can be present with appendicitis, inflammatory bowel disease, and other extrarenal disorders.

Most adults do not require assessment for structural abnormalities unless infections recur or are complicated, nephrolithiasis is suspected, there is painless hematuria or new renal insufficiency, or fever persists for ≥ 72 h. Imaging choices include ultrasonography, CT, and IVU. Occasionally, voiding cystourethrography, retrograde urethrography, or cystoscopy is warranted. Urologic investigation is not routinely needed in women with symptomatic or asymptomatic recurrent cystitis, because findings do not influence therapy. Children with UTI often require imaging (see p. 2846).

Treatment

- Antibiotics
- Occasionally surgery (eg, to drain abscesses, correct underlying structural abnormalities, or relieve obstruction)

All forms of bacterial UTI require antibiotics. Obstructive uropathy, anatomic abnormalities, and neuropathic urinary tract lesions such as compression of the spinal cord usually require surgical correction. Catheter drainage of an obstructed urinary tract aids in prompt control of UTI. Occasionally, a renal cortical abscess or perinephric abscess requires surgical drainage. Instrumentation of the lower urinary tract in the presence of infected urine should be deferred if possible. Sterilization of the urine before instrumentation and antibiotic therapy for 3 to 7 days after instrumentation can prevent life-threatening urosepsis. For patients with troublesome dysuria, phenazopyridine may help control symptoms until the antibiotics do (usually within 48 h).

Urethritis: Sexually active patients with symptoms are usually treated presumptively for STDs pending test results. A typical regimen is ceftriaxone 125 mg IM plus either azithromycin 1 g po once or doxycycline 100 mg po bid for 7 days. For non-STD urethritis in men, trimethoprim/sulfamethoxazole (TMP/SMX) or a fluoroquinolone is given for 10 to 14 days; women are treated with a regimen for cystitis.

Cystitis: A 3-day oral course of TMP/SMX or a fluoroquinolone effectively treats acute cystitis and eradicates potential bacterial pathogens in vaginal and GI reservoirs. Single-dose therapy results in higher recurrence rates and is not recommended. Longer courses of therapy (7 to 14 days) are prescribed for patients with a history of recent UTI, diabetes mellitus, or symptoms lasting > 1 wk.

If pyuria but not bacteriuria is present in a sexually active woman, then *C. trachomatis* urethritis is diagnosed presumptively, and appropriate treatment is given to the patient and her sex partner. If symptoms recur and culture reveals an organism sensitive to the drugs used for 3-day antibiotic therapy or if pyelonephritis is suspected, a 14-day course of TMP/SMX or a fluoroquinolone is given as for pyelonephritis.

Acute urethral syndrome: Acute urethral syndrome with pyuria is treated with doxycycline 100 mg po bid for 7 to 10 days or TMP/SMX 160/800 mg po bid for 3 days. If neither pyuria nor bacteriuria is present, antibiotics are not indicated. A course of urinary analgesics may be appropriate.

Asymptomatic bacteriuria: Ordinarily, asymptomatic bacteriuria in patients with diabetes, elderly patients, or patients with chronically indwelling bladder catheters should not be treated. However, asymptomatic bacteriuria in pregnant women is actively sought and treated as a symptomatic UTI, although many antibiotics cannot be safely used. Oral β-lactams, sulfonamides, and nitrofurantoin are considered safe in early pregnancy, but sulfonamides should be avoided near parturition because of a possible role in the development of kernicterus.

Treatment may also be indicated in asymptomatic UTI in patients with neutropenia, patients with recent renal transplantation, patients scheduled for instrumentation of the urinary tract (after removal of a bladder catheter that has been in place for > 1 wk), young children with gross VUR, and patients with frequent UTI symptoms from a struvite calculus that cannot be removed. Therapy typically consists of an appropriate antibiotic (based on culture results) for 3 to 14 days or long-term suppressive therapy for

untreatable obstructive problems (eg, calculi, reflux).

Acute pyelonephritis: Outpatient treatment with oral antibiotics is possible if the patient is reliable in following medical advice and is immunocompetent and has no nausea or vomiting, signs of volume depletion, or evidence of septicemia. Typical regimens are 14 days of TMP/SMX 160/800 mg po bid or ciprofloxacin 500 mg po bid. Otherwise, patients should be hospitalized and given parenteral therapy selected on the basis of local sensitivity patterns of the most common strains. Common regimens include ampicillin plus gentamicin, TMP/SMX and a fluoroquinolone, and broad-spectrum cephalosporins (eg, ceftriaxone). Aztreonam, β-lactam/β-lactam inhibitor combinations (ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam), and imipenem/cilastatin are generally reserved for patients with more complicated pyelonephritis (eg, obstruction, calculi, resistant bacteria, hospital-acquired infection) or recent urinary tract instrumentation. If parenteral therapy is required, it is continued until defer-vescence and other signs of clinical improvement occur. In > 80% of patients, improvement occurs within 72 h. Oral therapy can then begin, and the patient can be discharged for the remainder of the 14-day treatment course. For complicated cases, prolonged antibiotic suppression may be needed as well as urologic correction of anatomic defects.

When pyelonephritis is diagnosed during pregnancy, hospitalization and parenteral therapy with a β-lactam with or without an aminoglycoside is appropriate.

Prevention

In women who experience ≥ 3 UTIs/yr, voiding immediately after sexual intercourse and avoiding use of a diaphragm may be helpful. Drinking cranberry juice (50 mL of concentrate or about 300 mL of juice daily) reduces pyuria and bacteriuria. Increasing total fluid intake may also help.

If these techniques are unsuccessful, low-dose oral antibiotic prophylaxis greatly reduces the incidence of recurrent UTIs—eg, TMP/SMX 40/200 mg once/day or 3 times/wk, nitrofurantoin (macrocrystals) 50 or 100 mg once/day, or a fluoroquinolone (eg, ciprofloxacin, norfloxacin, ofloxacin, lome-floxacin, enoxacin). Long-term use of nitrofurantoin increases the risk of adverse effects and is contraindicated in patients with renal failure. Postcoital TMP/SMX or a fluoroquinolone may be effective. If UTI recurs after 6 mo of this therapy, prophylaxis may be reinstituted for 2 or 3 yr.

Because of potential injury to a fetus, users of fluoroquinolones should also use effective contraception. Some antibiotics (macrolides, tetracyclines, rifampin, metronidazole, penicillins, and TMP/SMX) interfere with the effectiveness of oral contraceptives by interrupting the enterohepatic recycling of estrogen or by inducing hepatic estrogen metabolism. Women who use oral contraceptives should use barrier contraceptives while they are taking these antibiotics.

In pregnant women, effective prophylaxis of UTI is similar to that in nonpregnant women. Appropriate patients include those with acute pyelonephritis during a pregnancy, patients with > 1 episode (despite treatment) of UTI or bacteriuria during pregnancy, and patients who required prophylaxis for recurrent UTI before pregnancy.

In postmenopausal women, antibiotic prophylaxis is similar to that described previously. Additionally, topical estrogen therapy markedly reduces the incidence of recurrent UTI in women with atrophic vaginitis or atrophic urethritis.

Bacterial Urinary Tract Infections in Patients With Indwelling Bladder Catheters

Patients with indwelling bladder catheters are predisposed to bacteriuria and UTIs. Symptoms may be vague or may suggest sepsis. Diagnosis depends on the presence of symptoms. Testing includes urinalysis and culture after the catheter has been removed and a new one inserted. The most effective preventive measures are avoiding unnecessary catheterization and removing catheters as soon as possible.

Bacteria can enter the bladder with the insertion of the catheter, through the catheter lumen, or from around the outside of the catheter. A biofilm develops around the outside of the catheter and on the

uroepithelium. Bacteria enter this biofilm, which protects them from the mechanical flow of urine, host defenses, and antibiotics, making bacterial elimination difficult. Even with thoroughly aseptic catheter care, the chance of developing significant bacteriuria every day the catheter is indwelling is 3 to 10%. Of patients who develop bacteriuria, 10 to 25% develop symptoms of UTI. Fewer develop symptoms of sepsis. Risk factors for UTI include duration of catheterization, female sex, diabetes mellitus, opening a closed system, and suboptimal aseptic techniques. Indwelling bladder catheters can also predispose to fungal UTI (see p. 2380).

UTI can also develop in women during the days after a catheter has been removed.

Symptoms and Signs

Patients with UTI who have indwelling catheters may not have symptoms typical of UTIs. Symptoms of lower tract UTI in patients with indwelling catheters may be caused by obstruction of the catheter, development of bladder stones, and periurinary tract infections. Symptoms of acute or chronic pyelonephritis may also develop without the typical urinary tract symptoms. Patients may have nonspecific symptoms such as malaise, fever, flank pain, anorexia, and sepsis with fever, altered mental status, decreased BP, and tachypnea.

Diagnosis

• Urinalysis and urine culture for patients with symptoms or at high risk of sepsis

Testing is done only in patients who have symptoms, because treatment of asymptomatic bacteriuria is not recommended except for patients at high risk of developing sepsis, such as patients with granulocytopenia, organ transplant patients taking immunosuppressants, pregnant women, and patients undergoing urologic surgery. Diagnostic testing includes urinalysis and urine culture. If bacteremia is suspected, blood cultures are done. Urine cultures should be taken by a direct needle stick of the catheter with aseptic technique, so that contamination of the specimen is minimized. Pyuria tends to predict bacteriuria but not necessarily symptoms of UTI or bacteremia, so whether to treat is a clinical decision.

Women who have had a catheter removed should receive urine culture within 48 h regardless of whether symptoms occur.

Treatment

• Antibiotics

Treatment includes antibiotics and supportive measures. A 14-day course of a fluoroquinolone is a reasonable empiric choice, depending on local resistance patterns. Antibiotic choice should be modified by the results of urine or blood culture and sensitivity testing. Asymptomatic women and men with recent catheter removal who have UTI diagnosed by urine culture should be treated based on the culture results.

Prevention

The most effective preventive measures are avoiding catheterization and removing catheters as soon as possible. Optimizing aseptic technique and maintaining a closed drainage system also reduce risk. Routine, periodic catheter replacement is not recommended. Routine use of prophylactic antibiotics is controversial: Fluoroquinolones may slightly decrease bacteriuria and symptomatic UTIs, although this finding is not firmly established. A recent study has shown a decrease in UTI using catheters impregnated with nitrofurazone in trauma patients. However, most patients with bacteriuria do not develop symptoms, and bacteriuria develops almost inevitably when antibiotics are stopped.

Chronic Pyelonephritis

(Chronic Infective Tubulointerstitial Nephritis)

Chronic pyelonephritis is chronic pyogenic infection of the kidney that occurs almost exclusively in patients with major anatomic abnormalities. Symptoms include fever, malaise, and flank pain. Diagnosis is with urinalysis, culture, and imaging tests. Treatment is with antibiotics and correction of any structural disorders.

Reflux of infected urine into the renal pelvis is the usual mechanism. Causes include obstructive uropathy, struvite calculi, and, most commonly, VUR.

Pathologically there is atrophy and calyceal deformity with overlying parenchymal scarring. The disease may progress to renal failure. Chronic pyelonephritis causes about 2 to 3% of end-stage renal disease. Patients with chronic pyelonephritis may have residual foci of infection that may predispose to bacteremia or, among kidney transplant patients, seed the urinary tract and transplanted kidney.

Xanthogranulomatous pyelonephritis (XPN) is an unusual variant that typically occurs in middle-aged women with a history of recurrent UTIs. It is a complication of obstruction due to renal calculi and is typically associated with *Proteus* infections. The kidney is enlarged, and perirenal fibrosis and adhesions to adjacent retroperitoneal structures are common. The disease is almost always unilateral and appears to represent an abnormal inflammatory response to infection. Giant cells, lipid-laden macrophages, and cholesterol clefts account for the yellow color of the infected tissue. The disease may also occur in children.

Symptoms and Signs

Symptoms and signs are often vague and inconsistent. Some patients have fever, flank or abdominal pain, malaise, or anorexia. In XPN, a unilateral renal mass can usually be palpated.

Diagnosis

• Urinalysis and urine culture

• Imaging

Chronic pyelonephritis is suspected in patients with a history of recurrent UTIs and acute pyelonephritis. However, most patients, except for children with VUR, do not have such a history. Sometimes the diagnosis is suspected because typical findings are incidentally noted on an imaging study. Symptoms, because they are vague and nonspecific, may not suggest the diagnosis.

Urinalysis and urine culture and usually imaging tests are done. On urinalysis, proteinuria is absent, minimal, or intermittent even when renal scarring is far advanced. Urinary sediment is usually scant, but renal epithelial cells, granular casts, and occasionally WBC casts are present. When both kidneys are involved, defects in concentrating ability and hyperchloremic acidosis may appear before significant azotemia occurs. Urine culture may be sterile or positive for gram-negative organisms.

Initial imaging is usually with ultrasonography or helical CT. The hallmark of chronic pyelonephritis (usually with reflux or obstruction) on imaging is classically a large, deep, segmental, coarse cortical scar usually extending to one or more of the renal calyces. The upper pole is the most common site. Initially, renal cortex is lost and the renal parenchyma thins. Uninvolved renal tissue may hypertrophy locally with segmental enlargement in patients with chronic pyelonephritis. Ureteral dilation may be present, reflecting the changes induced by chronic severe reflux. Similar changes can occur with urinary tract TB (see p. 1312). Other studies are not done routinely.

In XPN, urinalysis and urine culture indicate the presence of infection, but diagnosis is confirmed by radiologic examination. CT can exclude renal carcinoma and other lesions and is preferred over IVU. Blood tests reveal nonspecific findings including anemia and mild liver dysfunction.

Prognosis

The course of chronic pyelonephritis is extremely variable, but the disease typically progresses very slowly. Most patients have adequate renal function for ≥ 20 yr after onset. Frequent exacerbations of acute pyelonephritis, although controlled, usually further deteriorate renal structure and function. Continued obstruction predisposes to or perpetuates pyelonephritis and increases intrapelvic pressure, which damages the kidney directly.

Treatment

If obstruction cannot be eliminated and recurrent UTIs are common, long-term therapy with antibiotics (eg, TMP/SMX, trimethoprim, a fluoroquinolone, nitrofurantoin) is useful and may be required indefinitely. Complications of uremia or hypertension must be treated appropriately.

For XPN, an initial course of antibiotics should be given to control local infection, followed by en bloc nephrectomy with removal of all involved tissue and closure of any fistulas.

Patients undergoing renal transplantation who have chronic pyelonephritis may require nephrectomy before the transplant.

Fungal Urinary Tract Infections

Fungal infections of the urinary tract primarily affect the bladder and kidneys.

Species of *Candida*, the most common cause, are normal commensals in humans. *Candida* colonization differs from infection in that infection produces tissue reaction. All invasive fungi (eg, *Cryptococcus neoformans*, *Aspergillus* sp, *Mucoraceae* sp, *Histoplasma capsulatum*, *Blastomyces* sp, *Coccidioides immitis*) may infect the kidneys as part of systemic or disseminated mycotic infection (see p. 1318). Their presence alone indicates infection.

Lower UTI with *Candida* usually occurs with urinary catheters, typically after bacteriuria and antibiotic therapy, although candidal and bacterial infections frequently occur simultaneously. *C. albicans* prostatitis occurs infrequently in patients with diabetes, usually after instrumentation.

Renal candidiasis is usually spread hematogenously and commonly originates from the GI tract. Ascending infection is possible and occurs mainly in patients with nephrostomy tubes, other permanent indwelling devices, and stents. At high risk are patients who are immunocompromised because of tumor, AIDS, chemotherapy, or immunosuppressants. A major source of candidemia in such high-risk hospitalized patients is an in-dwelling intravascular catheter. Renal transplantation increases the risk because of the combination of indwelling catheters, stents, antibiotics, anastomotic leaks, obstruction, and immunosuppressive therapy.

Complications of candidal infection can include emphysematous cystitis or pyelonephritis and fungus balls in the renal pelvis, ureter, or bladder. Bezoars may form in the bladder. Lower or upper tract obstruction may occur. Papillary necrosis and intrarenal and perinephric abscesses may form. Although renal function often declines, severe renal failure is rare without postrenal obstruction.

Symptoms and Signs

Most patients with candiduria are asymptomatic. Whether *Candida* can cause urethral symptoms (mild urethral itching, dysuria, watery discharge) in men is uncertain. Rarely, dysuria in women is caused by candidal urethritis, but it may result from the urine coming into contact with periurethral tissue that is inflamed due to candidal vaginitis.

Among **lower UTIs**, cystitis due to *Candida* may result in frequency, urgency, dysuria, and suprapubic pain. Hematuria is common, and, in patients with poorly controlled diabetes, pneumaturia due to emphysematous cystitis has occurred. Fungus balls or bezoars may cause symptoms of urethral obstruction.

With **renal candidiasis** that is hematogenously spread, most patients lack symptoms referable to the

kidney but may have antibiotic-resistant fever, candiduria, and unexplained deteriorating renal function. Fungus ball elements in the ureter and renal pelvis frequently cause hematuria and urinary obstruction. Occasionally, papillary necrosis or intrarenal or perinephric abscesses cause pain, fever, hypertension, and hematuria. Patients may have manifestations of candidiasis in other sites (eg, CNS, skin, eyes, liver, spleen).

Diagnosis

• Urine culture

• Evidence of tissue reaction (in cystitis) or pyelonephritis

Candida UTI is considered in patients with predisposing factors and symptoms suggesting UTI and in all patients with candidemia. *Candida* should be suspected in men with symptoms of urethritis only when all other causes of urethritis have been excluded.

Diagnosis of *Candida* UTI is by culture, usually from urine. The level at which candiduria reflects true *Candida* UTI and not merely colonization or contamination is unknown. Differentiating *Candida* colonization from infection requires evidence of tissue reaction.

Cystitis is usually diagnosed in high-risk patients with candiduria by the presence of bladder inflammation or irritation, as evidenced by pyuria. Cystoscopy and ultrasonography of the kidney and bladder may help detect bezoars and obstruction.

Renal candidiasis is considered in patients with fever, candiduria, or passage of fungus balls. Severe renal failure suggests postrenal obstruction. Imaging of the urinary tract may help reveal the degree of involvement. Blood cultures for *Candida* are often negative.

Unexplained candiduria should prompt evaluation of the urinary tract for structural abnormalities.

Treatment

• Only for symptomatic or high-risk patients

• Antifungal drugs

Fungal colonization of catheters does not require treatment. Asymptomatic candiduria rarely requires therapy. Candiduria should be treated in the following:

• Symptomatic patients

• Neutropenic patients

• Patients with renal allografts

• Patients who are undergoing urologic manipulation

Urinary stents and Foley catheters should be removed (if possible). Treatment with fluconazole (200 mg po once/day for 7 to 14 days) and with IV amphotericin B (see p. 1319) has been successful. In the absence of renal insufficiency, flucytosine (25 mg/kg po qid) may help eradicate candiduria due to non-albicans species of *Candida*; however, resistance may emerge rapidly when this compound is used alone. Bladder irrigation with amphotericin B may transiently clear candiduria but is rarely indicated. Even with apparently successful local or systemic antifungal therapy for candiduria, relapse is frequent, and this likelihood is increased by continued use of a urinary catheter.

In patients with **renal candidiasis**, IV amphotericin B and high-dose oral fluconazole (≥ 400 mg/day) are equally effective in the primary treatment of invasive infection with *C. albicans* and *C. tropicalis*. Even when amphotericin B is used initially, oral fluconazole should be substituted early in the course of

treatment. However, some less common *Candida* species are not susceptible to fluconazole.

Chapter 234. Cystic Kidney Disease

Introduction

Cystic kidney disease may be congenital or acquired. Congenital disorders may be inherited as autosomal dominant disorders or autosomal recessive disorders or have other causes (eg, sporadic mutations, chromosomal abnormalities, teratogens). Some are part of a malformation syndrome—see Table 234-1).

Acquired Renal Cysts

Acquired renal cysts are simple cysts that must be distinguished from more serious causes of cystic disease.

Acquired cysts are usually simple, ie, they are round and sharply demarcated with smooth walls. They may be solitary or multiple.

Solitary cysts: Isolated cysts are most often detected incidentally on imaging studies; they are distinguished from other cystic renal disorders and renal masses, such as renal cell carcinoma, which is typically irregular or multiloculated with irregular walls, septae, and areas of unclear demarcation. Their cause is unknown. They are generally clinically insignificant but rarely can cause hematuria or become infected.

Multiple cysts: Multiple cysts are most common in patients with chronic kidney disease, especially patients undergoing dialysis. Cause is unknown, but the cysts may be due to compensatory hyperplasia of residually functioning nephrons. Usual criterion for diagnosis is ≥ 4 cysts in each kidney detected with ultrasonography or CT. Multiple acquired cysts (acquired cystic disease) can usually be differentiated from autosomal dominant polycystic kidney disease by the absence of family history and by small or normal-sized kidneys.

Acquired cysts are usually asymptomatic, but occasional patients develop hematuria, renal or perirenal hemorrhage, infection, or flank pain. Acquired cysts are significant mainly because patients have a higher incidence of renal cell carcinoma; whether the cysts become malignant is unknown. For this reason, some physicians periodically screen patients with acquired cysts for renal carcinoma using ultrasonography or CT. Cysts that cause persistent bleeding or infection may require percutaneous drainage or, rarely, partial or complete nephrectomy.

Congenital Renal Cystic Dysplasia

Congenital renal cystic dysplasia is a broad category of congenital malformations involving metanephric malformation or congenital obstructive uropathies.

Congenital renal cystic dysplasia affects one or both kidneys. Renal cystic dysplasia may be an isolated congenital anomaly, or it may be part of a malformation syndrome (ie, associated with other clinical features—see Table 234-1). Associated urologic abnormalities may include ureteropelvic and

[**Table 234-1.** Major Groups of Cystic Nephropathies]

ureterovesicular junction obstruction, neurogenic bladder, ureterocele, posterior urethral valves, and prune-belly syndrome (a triad of abdominal wall muscle defects, urinary tract abnormalities [eg, dilated ureters, enlarged bladder and urethra], and bilateral cryptorchidism—see p. 2988).

Symptoms and signs vary by how much renal parenchyma is preserved and whether involvement is unilateral or bilateral. Some degree of renal insufficiency or renal failure may develop. Congenital renal cystic dysplasia is commonly discovered by ultrasonography prenatally or during early childhood.

Prognosis is highly unpredictable due to an inability to quantify residual functional parenchyma. Treatment is surgical correction of any associated GU abnormalities and, if renal insufficiency or renal

failure is present, renal replacement therapy.

Medullary Sponge Kidney

Medullary sponge kidney is formation of diffuse, bilateral medullary cysts caused by abnormalities in pericalyceal terminal collecting ducts.

The cause of medullary sponge kidney is unknown, but genetic transmission occurs in < 5% of cases.

Most patients are asymptomatic, and the disorder usually remains undiagnosed. It predisposes to calculus formation and UTI, so the most common presenting symptoms are the following:

• Renal colic

• Hematuria

• Dysuria

Medullary sponge kidney is benign, and long-term prognosis is excellent. Obstruction by renal calculi may transiently reduce GFR and increase serum creatinine.

Diagnosis

• CT or IVU

The diagnosis is suspected in patients with recurrent calculi or UTIs or on the basis of incidental radiographic findings. Urinalysis typically shows evidence of incomplete distal renal tubular acidosis (overt metabolic acidosis is rare) and decreased urine-concentrating ability in patients without symptomatic polyuria.

Diagnosis is generally confirmed by CT, but IVU can be used. Ultrasonography is not helpful because cysts are small and located deep in the medulla.

Treatment

Treatment is indicated only for UTIs and for recurrent calculus formation. Thiazide diuretics (eg, hydrochlorothiazide 25 mg po bid) and high fluid intake inhibit calculus formation and may reduce incidence of obstructive complications in patients with recurrent calculi.

Nephronophthisis and Medullary Cystic Kidney Disease Complex

Nephronophthisis and medullary cystic kidney disease are inherited disorders that cause cysts restricted to the renal medulla or corticomedullary border and, eventually, end-stage renal disease.

Nephronophthisis and medullary cystic kidney disease are grouped together because they share many features. Pathologically, they cause cysts restricted to the renal medulla or corticomedullary border, as well as a triad of tubular atrophy, tubular basement membrane disintegration, and interstitial fibrosis. They probably share similar mechanisms, although these are not well characterized. Features of both disorders include the following:

• An ADH (vasopressin)-resistant urine-concentrating defect that leads to polyuria and polydipsia

• Na wasting severe enough to require supplementation

• Anemia

• A tendency toward mild proteinuria and a benign urinary sediment

• Eventually, end-stage renal disease

Key differences between nephronophthisis and medullary cystic kidney disease include inheritance patterns and age at onset of chronic kidney disease.

Nephronophthisis

Inheritance is autosomal recessive. Nephronophthisis accounts for up to 15% of chronic kidney disease with renal failure in children and young adults (< 20 yr). There are 3 types: infantile (median age at onset 1 yr), juvenile (median age at onset 13 yr), and adolescent (median age at onset 19 yr).

Nine gene mutations have been identified in patients with nephronophthisis. Mutations of the *NPHP1* gene are the most common, identified in about 30 to 60% of patients. About 10% of patients with nephronophthisis also have other manifestations, including retinitis pigmentosa, hepatic fibrosis, intellectual disability, and other neurologic abnormalities.

End-stage renal disease often develops during childhood and causes growth retardation and bone disease. However, in many patients, these problems develop slowly over years and are so well compensated for that they are not recognized as abnormal until significant uremic symptoms appear. Hypertension sometimes develops.

Diagnosis

• Imaging, genetic testing, or both

The diagnosis should be suspected in children with the following, particularly if the urinary sediment is benign:

• Polydipsia and polyuria

• Progressively decreasing renal function, particularly without hypertension

• Associated extrarenal findings

Proteinuria is usually absent. Diagnosis is confirmed by imaging, but cysts often occur only late in disease. Ultrasonography, CT, or MRI may show smooth renal outlines with normal-sized or small kidneys, loss of corticomedullary differentiation, and multiple cysts at the corticomedullary junction. Hydronephrosis is typically absent. Genetic testing is available.

Treatment

• Supportive care

In early disease, treatment involves management of hypertension, electrolyte and acid-base disorders, and anemia. Children with growth retardation may respond to nutritional supplements and growth hormone therapy. Ultimately, all patients develop renal failure and require dialysis or transplantation.

Medullary Cystic Kidney Disease

Inheritance is autosomal dominant. The disease affects people in their 30s through 70s. There are 2 types, which differ by median age at onset (type 1, 62 yr; type 2, also known as familial juvenile hyperuricemic nephropathy, 32 yr) and by genetic mutation (type 1 is localized to chromosome 1; type 2, to chromosome 16). About 15% of patients have no family history, suggesting a sporadic new mutation. Hypertension is common. Hyperuricemia and gout are the only extrarenal manifestations; they tend to develop early in type 2 and late in type 1. End-stage renal disease typically develops at age 30 to 50.

Medullary cystic kidney disease should be suspected in patients with the following, particularly if the

urinary sediment is benign:

• Polydipsia and polyuria

• Gout at a young age

• Family history of gout and chronic kidney disease

Mild proteinuria is possible. Results of imaging studies have many similarities to that of nephronophthisis; however, renal medullary cysts are only sometimes visible. Genetic testing can confirm the diagnosis of type 2. Kidney biopsy may be necessary for diagnosis of type 1.

Treatment is generally similar to that of nephronophthisis. Allopurinol can help control gout.

Autosomal Dominant Polycystic Kidney Disease

Polycystic kidney disease (PKD) is a hereditary disorder of renal cyst formation causing gradual enlargement of both kidneys, sometimes with progression to renal failure. Almost all forms are caused by a familial genetic mutation. Symptoms and signs include flank and abdominal pain, hematuria, and hypertension. Diagnosis is by CT or ultrasonography. Treatment is symptomatic before renal failure and with dialysis or transplantation afterward.

Etiology

Inheritance of PKD is autosomal dominant or recessive; sporadic cases occur rarely. Autosomal dominant polycystic kidney disease (ADPKD) has an incidence of 1/1000 and accounts for about 5% of patients with end-stage renal disease requiring replacement therapy. Clinical manifestations are rare before adulthood, but penetrance is essentially complete; all patients ≥ 80 yr have some signs. In contrast, autosomal recessive PKD is rare; incidence is 1/10,000. It frequently causes renal failure during childhood (see p. 2982).

In 86 to 96% of cases, ADPKD is caused by mutations in the *PKD1* gene on chromosome 16, which codes for the protein polycystin 1; most other cases are caused by mutations in the *PKD2* gene on chromosome 4, which codes for polycystin 2. A few familial cases are unrelated to either locus.

Pathophysiology

Polycystin 1 may regulate tubular epithelial cell adhesion and differentiation; polycystin 2 may function as an ion channel, with mutations causing fluid secretion into cysts. Mutations in these proteins may alter the function of renal cilia, which enable tubular cells to sense flow rates. A leading hypothesis proposes that tubular cell proliferation and differentiation are linked to flow rate and that ciliary dysfunction may thus lead to cystic transformation.

Early in the disorder, tubules dilate and slowly fill with glomerular filtrate. Eventually, the tubules separate from the functioning nephron and fill with secreted rather than filtered fluid, forming cysts. Hemorrhage into cysts may occur, causing hematuria; patients are also at higher risk of acute pyelonephritis and urinary calculi (in 20%). Vascular sclerosis and interstitial fibrosis eventually develop via unknown mechanisms and typically affect < 10% of tubules; nonetheless, renal failure develops in about 35 to 45% of patients by age 60.

Extrarenal manifestations are common:

• Most patients have hepatic cysts, which typically do not affect liver function.

• Patients also have a higher incidence of pancreatic and intestinal cysts, colonic diverticula, and inguinal and abdominal wall hernias.

• Valvular heart disorders (most often mitral valve prolapse and aortic regurgitation) can be detected by

cardiac ultrasonography in 25 to 30% of patients; other valvular disorders may be due to collagen abnormalities.

- Aortic regurgitation results from aortic root dilation due to arterial wall changes (including aortic aneurysm).

- Coronary artery aneurysms occur.

- About 4% of young adults and up to 10% of elderly patients have cerebral aneurysms. Aneurysms rupture in 65 to 75% of patients, usually before age 50; risk factors include family history of aneurysm or rupture, larger aneurysms, and poorly controlled hypertension.

Symptoms and Signs

ADPKD usually causes no symptoms initially; one half of patients remain asymptomatic, never develop renal insufficiency or failure, and are never diagnosed. Most patients who develop symptoms do so by the end of their 20s. Symptoms include low-grade flank, abdominal, and lower back pain due to cystic enlargement and symptoms of infection. Acute pain, when it occurs, is usually due to hemorrhage into cysts or passage of a calculus; fever is common with acute pyelonephritis. Hepatic cysts may cause right upper quadrant pain if they enlarge or become infected. Valvular disorders rarely cause symptoms but occasionally cause heart failure and require valvular replacement. Symptoms and signs of unruptured cerebral aneurysm can be absent or may include headache, nausea and vomiting, and cranial nerve deficits; these manifestations warrant immediate intervention (see Sidebar 173-1 on p. 1653).

Signs are nonspecific and include hematuria and hypertension (each in about 40 to 50%) and proteinuria (in 20%). Anemia is less common than in other types of chronic renal failure, presumably because erythropoietin production is preserved. In advanced disease, the kidneys may become grossly enlarged and palpable, causing fullness in the upper abdomen and flank.

Diagnosis

- Ultrasonography

- Sometimes CT or MRI or genetic testing

The diagnosis is suspected in patients with the following:

- A positive family history

- Typical symptoms or signs

- Cysts detected incidentally on imaging studies

Patients should be counseled before undergoing diagnostic testing, particularly if they are asymptomatic. For example, many authorities recommend against testing asymptomatic young patients because no disease-modifying treatment is effective at this age and diagnosis has potential negative effects on ability to obtain health insurance and on mood. Diagnosis is usually by imaging, showing extensive cystic changes throughout the kidneys and a moth-eaten appearance due to cysts that displace functional tissue. These changes develop with age and are less often present or obvious in younger patients. Ultrasonography is usually done first. If ultrasonography results are inconclusive, CT or MRI, which are both more sensitive (particularly when done using contrast), is done. Urinalysis, renal function tests, and CBC are done, but results are not specific.

Urinalysis detects mild proteinuria and microscopic or macroscopic hematuria. Gross hematuria may be due to a dislodged calculus or to hemorrhage from a ruptured cyst. Pyuria is common even without bacterial infection. Initially, BUN and creatinine are normal or only mildly elevated, but they slowly increase, especially when hypertension is present. Rarely, CBC detects polycythemia.

Patients with symptoms of cerebral aneurysm require high-resolution CT or magnetic resonance angiography. However, there is no consensus on whether asymptomatic patients should be screened for cerebral aneurysm, at what age, and how often. A reasonable approach is to screen patients with ADPKD and a family history of hemorrhagic stroke or cerebral aneurysm.

Genetic testing for PKD mutations is currently reserved for any of the following:

- Patients with suspected PKD and no known family history
- Patients with inconclusive results on imaging
- Younger patients (eg, age < 30, in whom imaging results are often inconclusive) in whom the diagnosis must be made (eg, a potential kidney donor)

Genetic counseling is recommended for 1st-degree relatives of patients with ADPKD.

Prognosis

By age 75, 50 to 75% of patients with ADPKD require renal replacement therapy (dialysis or transplantation). Predictors of more rapid progression to renal failure include the following:

- Earlier age at diagnosis
- Male sex
- Sickle cell trait
- *PKD1* genotype
- Larger or rapidly increasing kidney size
- Gross hematuria
- Hypertension

ADPKD does not increase risk of renal cancer, but if patients with ADPKD develop renal cancer, it is more likely to be bilateral. Renal cancer rarely causes death. Patients usually die of heart disease (sometimes valvular), disseminated infection, or ruptured cerebral aneurysm.

Treatment

- Control of risk factors
- Supportive measures

Strict BP control is essential. UTIs should be treated promptly. Percutaneous aspiration of cysts may help manage severe pain due to hemorrhage or compression but has no effect on long-term outcome. Nephrectomy is an option to relieve severe symptoms due to massive kidney enlargement (eg, pain, hematuria) or recurrent UTIs. Hemodialysis, peritoneal dialysis, or kidney transplantation is required in patients who develop chronic renal failure. ADPKD does not recur in grafts. With dialysis, patients with ADPKD maintain higher Hb levels than any other group of patients with renal failure.

Chapter 235. Glomerular Disorders

Introduction

Glomerular disorders are classified as those that manifest predominantly with hematuria (nephritic syndrome), high-level proteinuria (nephrotic syndrome), or both. Disorders tend to manifest at different ages (see Table 235-1) although there is much overlap. The disorders may be primary or have secondary causes (see Tables 235-2 and 235-4).

The pathophysiology of nephritic and nephrotic disorders differs substantially, but their clinical overlap is considerable—eg, several disorders may manifest with the same clinical picture—and the presence of hematuria or proteinuria does not itself predict response to treatment or prognosis.

A glomerular disorder is usually suspected when screening or diagnostic testing reveals an elevated serum creatinine level and abnormal urinalysis (hematuria with or without casts, proteinuria, or both). Approach to the patient involves distinguishing predominant-nephritic from predominant-nephrotic features and identifying likely causes by patient age, accompanying illness (see Tables 235-1 and 235-4), and other elements of the history (eg, time course, systemic manifestations, family history).

Renal biopsy is indicated when diagnosis is unclear from history or when histology influences choice of treatment and outcomes (eg, lupus nephritis).

Nephritic Syndrome

Nephritic syndrome is defined by hematuria and the presence of dysmorphic RBCs and RBC casts on microscopic examination of urinary sediment. Often ≥ 1 of the following elements are present: mild to moderate proteinuria, edema, hypertension, elevated serum creatinine, and oliguria. It has both primary and secondary causes. Diagnosis is based on history, physical examination, and sometimes renal biopsy. Treatment and prognosis vary by cause.

Nephritic syndrome is a manifestation of glomerular inflammation (glomerulonephritis [GN]) and occurs at any age. Causes differ by age (see Table 235-1), and mechanisms differ by cause. The syndrome can be acute or chronic and primary (idiopathic) or secondary.

Postinfectious GN is the prototype of acute GN, but the condition may be caused by other glomerulopathies and by systemic disorders such as connective tissue disorders and hematologic dyscrasias (see Table 235-2). Chronic GN has features similar to those of acute GN but develops slowly and may cause mild to moderate proteinuria. Examples include IgA nephropathy and hereditary nephritis.

Hereditary Nephritis

(Alport's Syndrome)

Hereditary nephritis is a genetically heterogenous disorder characterized by hematuria,

[**Table 235-1.** Glomerular Disorders by Age and Presentation]

impaired renal function, sensorineural deafness, and ocular abnormalities. Cause is a gene mutation affecting type IV collagen. Symptoms and signs are those of nephritic syndrome (ie, hematuria, eventual renal insufficiency) often with sensorineural deafness and, less commonly, ophthalmologic symptoms. Diagnosis is by history, including family history, urinalysis, and biopsy (renal or skin). Treatment is the same as that of chronic kidney disease.

Hereditary nephritis is caused by a mutation in the *COL4A5* gene that encodes the α-5 chain of type IV collagen and results in altered type IV collagen strands. The mechanism by which collagen alteration

causes a glomerular disorder is unknown, but impaired structure and function are presumed; in most families, thickening and thinning of the glomerular and tubular basement membranes occur, with multilamination of the lamina densa in a focal or local distribution. Glomerular scarring and interstitial fibrosis eventually result.

The disorder is most commonly inherited in X-linked fashion, although autosomal recessive varieties exist. There are 2 forms: a juvenile form with onset of renal insufficiency between ages 20 and 30 yr and an adult form with onset of renal insufficiency after age 30.

Symptoms and Signs

Because of X-linked transmission, women usually are asymptomatic and have little functional impairment. Most men eventually develop renal symptoms and signs similar to those of acute nephritic syndrome (eg, microscopic hematuria, eventually gross hematuria) and progress to renal insufficiency between ages 20 and 30 (juvenile form).

Sensorineural deafness frequently is present, affecting higher frequencies; it may

[Table 235-2. Causes of Glomerulonephritis]

not be noticed during early childhood. Some men develop renal insufficiency after age 30 (adult form) with deafness that occurs late or is mild. Some patients have sensorineural deafness alone without renal disease but can transmit renal disease to their children.

Ophthalmologic abnormalities—cataracts (most common), anterior lenticonus (a regular conical protrusion on the anterior aspect of the lens due to thinning of the lens capsule), spherophakia (spherical lens deformation that can predispose to lens subluxation), nystagmus, retinitis pigmentosa, blindness—also occur but less frequently than deafness.

Other nonrenal manifestations include polyneuropathy and thrombocytopenia.

Diagnosis

• Clinical findings and urinalysis

• Renal biopsy

Diagnosis is suggested in patients who have microscopic hematuria on urinalysis or recurrent episodes of gross hematuria, particularly if an abnormality of hearing or vision or a family history of chronic kidney disease is present.

Urinalysis and usually renal biopsy are done. The urine may contain small amounts of protein, WBCs, and casts of various types. Nephrotic syndrome occurs rarely. No distinguishing histologic changes are seen on light microscopy. The diagnosis can be confirmed by any of the following:

• Renal biopsy with immunostaining for the subtypes of type IV collagen

• Characteristic disorganization of the lamina densa of the glomerular capillary seen using electron microscopy

• Skin biopsy with immunostaining for the type IV collagen subtypes in a patient with a positive family history

A combination of immunostaining and electron microscopy is often needed to distinguish hereditary nephritis from some forms of thin basement membrane disease. Although not yet widely available, molecular techniques for evaluating DNA gene mutations or mRNA may become the diagnostic techniques of choice.

Treatment

• Same as that for other causes of chronic kidney disease

Treatment is indicated only when uremia occurs; its management is the same as that for other causes of chronic kidney disease (see p. 2444). Anecdotal reports suggest that ACE inhibitors or angiotensin II receptor blockers may slow progression of renal disease. Transplantation has been successful. Genetic counseling is indicated.

Immunoglobulin A Nephropathy

IgA nephropathy is deposition of IgA immune complexes in glomeruli, manifesting as slowly progressive hematuria, proteinuria, and, often, renal insufficiency. Diagnosis is based on urinalysis and renal biopsy. Prognosis is generally good. Treatment options include ACE inhibitors, angiotensin II receptor blockers, corticosteroids, immunosuppressants, and ω-3 polyunsaturated fatty acids.

IgA nephropathy is a form of chronic GN characterized by the deposition of IgA immune complexes in glomeruli. It is the most common form of GN worldwide. It occurs at all ages, with a peak onset in the teens and 20s; affects men 2 to 6 times more frequently than women; and is more common in whites and Asians than in blacks. Prevalence estimates for IgA kidney deposits are 5% in the US, 10 to 20% in southern Europe and Australia, and 30 to 40% in Asia. However, some people with IgA deposits do not develop clinical disease.

Cause is unknown, but evidence suggests that there may be several mechanisms, including increased IgA1 production, defective IgA1 glycosylation causing increased binding to mesangial cells, decreased IgA1 clearance, a defective mucosal immune system, and overproduction of cytokines stimulating mesangial cell proliferation. Familial clustering has also been observed, suggesting genetic factors at least in some cases.

Renal function is initially normal, but symptomatic renal disease may develop. A few patients present with acute renal failure or chronic kidney disease, severe hypertension, or nephrotic syndrome.

Symptoms and Signs

The most common manifestation is persistent or recurrent macroscopic hematuria (90% of involved children) or asymptomatic microscopic hematuria with mild proteinuria. Other symptoms are usually not prominent.

Gross hematuria usually begins 1 or 2 days after a febrile mucosal (upper respiratory, sinus, enteral) illness, thus mimicking acute postinfectious glomerulonephritis, except the onset of hematuria is earlier (coinciding with or immediately after the febrile illness). Rapidly progressive GN is the initial manifestation in < 10% of patients.

Diagnosis

• Clinical findings and urinalysis

• Sometimes renal biopsy

Diagnosis is suggested by any of the following:

• Gross hematuria, particularly within 2 days of a febrile mucosal illness or with flank pain

• Incidentally noted findings on urinalysis

• Occasionally, rapidly progressive GN

When manifestations are moderate or severe, diagnosis is confirmed by biopsy.

Urinalysis demonstrates microscopic hematuria, usually with dysmorphic RBCs and RBC casts. Mild proteinuria (< 1 g/day) is typical and may occur without hematuria; nephrotic syndrome develops in ≤ 20%. Serum creatinine level is usually normal.

Renal biopsy shows granular deposition of IgA and complement (C3) on immunofluorescent staining in an expanded mesangium with foci of segmental proliferative or necrotizing lesions. Importantly, mesangial IgA deposits are nonspecific and also occur in many other disorders, including Henoch-Schonlein purpura, cirrhosis, inflammatory bowel disease, psoriasis, HIV infection, lung cancer, and several connective tissue disorders. Glomerular IgA deposition is a primary feature of Henoch-Schonlein purpura, and the 2 disorders may be indistinguishable based on biopsy specimens, leading to speculation that Henoch-Schonlein purpura may be a systemic form of IgA nephropathy. However, Henoch-Schonlein purpura is clinically distinct from IgA nephropathy, usually manifesting as purpuric rash, arthralgias, and abdominal pain (see p. 321).

Other serum immunologic tests are usually unnecessary. Complement concentrations are usually normal. Plasma IgA concentration may be elevated and circulating IgA-fibronectin complexes are present; however, these findings are not helpful diagnostically.

Prognosis

IgA nephropathy usually progresses slowly; renal insufficiency and hypertension develop within 10 yr in 15 to 20% of patients. Progression to end-stage renal disease occurs in 25% of patients after 20 yr. When IgA nephropathy is diagnosed in childhood, prognosis is usually good. However, persistent hematuria invariably leads to hypertension, proteinuria, and renal insufficiency. Risk factors for progressive deterioration in renal function include the following:

- Proteinuria > 500 mg/24 h for > 6 mo
- Elevated creatinine
- Uncontrolled hypertension
- Microscopic hematuria for > 6 mo
- Extensive fibrotic changes in the glomerulus or interstitium
- Crescents on biopsy

Treatment

- Often ACE inhibitors or angiotensin II receptor blockers for hypertension, creatinine > 1.2 mg/dL, or urinary protein > 1 g/day
- Corticosteroids and possibly immunosuppressants for progressive disease, urinary protein > 2 g/day, or creatinine clearance < 60 mL/min
- Transplantation rather than dialysis if possible

Normotensive patients with intact renal function (creatinine < 1.2 mg/dL) and only mild proteinuria (< 0.5 g/day) usually are not treated. Patients with renal insufficiency or more severe proteinuria and hematuria are usually offered treatment, which ideally should be started before significant renal insufficiency develops.

Angiotensin inhibition: ACE inhibitors or angiotensin II receptor blockers are used on the premise that they reduce BP, proteinuria, and glomerular fibrosis. Patients with the DD genotype for the ACE gene may be at greater risk of disease progression but may also be more likely to respond to ACE inhibitors or

angiotensin II receptor blockers. For patients with hypertension, ACE inhibitors or angiotensin II receptor blockers are the antihypertensives of choice even for relatively mild chronic kidney disease.

Corticosteroids and immunosuppressants: Corticosteroids have been used for many years, but benefit is not well documented. One protocol uses methylprednisolone 1 g IV once/day for 3 days at the beginning of months 1, 3, and 5 plus prednisone 0.5 mg/kg po every other day for 6 mo. Because of the risk of adverse effects, corticosteroids should probably be reserved for patients with any of the following:

• Progression, as shown by worsening proteinuria or renal function

• Heavy proteinuria (> 2 g/day)

• Significant renal insufficiency (creatinine clearance < 60 mL/min)

Combinations of corticosteroids, cyclophosphamide, and azathioprine are also used, but efficacy and safety compared with corticosteroids alone are uncertain. Mycophenolate mofetil is under investigation. None of these drugs, however, prevents recurrence in transplant patients.

Other treatments: ω-3 Polyunsaturated fatty acids (eg, 4 to 12 g/day), available in fish oil supplements, have been used to treat IgA nephropathy, but data on efficacy are contradictory. Mechanism of effect may include alterations in inflammatory cytokines.

Other interventions have been tried to lower IgA overproduction and to inhibit mesangial proliferation. Elimination of gluten, dairy products, eggs, and meat from the diet; tonsillectomy; and immune globulin (1 g/kg IV 2 days/mo for 3 mo followed by immune globulin 0.35 mL/kg of 16.5% solution IM q 2 wk for 6 mo) all theoretically reduce IgA production. Heparin, dipyridamole, and statins are just a few examples of in vitro mesangial cell inhibitors. Data supporting any of these interventions are limited or absent, and none can be recommended for routine treatment.

Renal transplantation is better than dialysis because of excellent long-term disease-free survival. The condition recurs in ≤ 15% of graft recipients.

Postinfectious Glomerulonephritis

Postinfectious glomerulonephritis (PIGN) occurs after infection, usually with a nephritogenic strain of group A β-hemolytic streptococcus. Diagnosis is suggested by history and urinalysis and confirmed by finding a low complement level and sometimes by antibody testing. Prognosis is excellent. Treatment is supportive.

Etiology

PIGN is the most common cause of a glomerular disorder in children between 5 and 15 yr; it is rare in children < 2 yr and uncommon in adults > 40 yr.

Most cases are caused by nephritogenic strains of group A β-hemolytic streptococci, most notably type 12 (which causes pharyngitis) and type 49 (which causes impetigo); an estimated 5 to 10% of patients with streptococcal pharyngitis and about 25% of those with impetigo develop PIGN. A latency period of 6 to 21 days between infection and GN onset is typical, but latency may extend up to 6 wk.

Less common pathogens are nonstreptococcal bacteria, viruses, parasites, rickettsiae, and fungi (see Table 235-2). Bacterial endocarditis and ventriculoatrial shunt infections are additional important conditions in which PIGN develops; ventriculoperitoneal shunts are more resistant to infection.

The mechanism is unknown, but microbial antigens are thought to bind to the glomerular basement membrane and activate complement both directly and via interaction with circulating antibodies, causing glomerular damage, which may be focal or diffuse.

Symptoms and Signs

Symptoms and signs range from asymptomatic hematuria (in about 50%) and mild proteinuria to full-blown nephritis with microscopic or gross hematuria (cola-colored, brown, smoky, or frankly bloody urine), proteinuria, oliguria, edema, hypertension, and renal insufficiency. Severe, late disease is a relatively uncommon cause of nephrotic syndrome. Renal failure that causes fluid overload with heart failure and urgent or malignant hypertension and requires dialysis affects 1 to 2% of patients and may manifest as a pulmonary-renal syndrome with hematuria and hemoptysis (see p. 1990). Fever is unusual and suggests persistent infection.

Clinical manifestations of nonstreptococcal PIGN may mimic other disorders (eg, polyarteritis nodosa, renal emboli, antimicrobial drug-induced acute interstitial nephritis).

Diagnosis

• Clinical evidence of recent infection

• Urinalysis showing GN

• Often hypocomplementemia

Streptococcal PIGN is suggested by history of pharyngitis or impetigo plus either typical symptoms of PIGN or incidental findings on urinalysis. Tests done to confirm the diagnosis depend on clinical findings. Antistreptolysin O, antihyaluronidase, and antideoxyribonuclease (anti-DNAase) antibodies are commonly measured. Serum creatinine and complement levels (C3 and total hemolytic complement activity) are also usually measured; however, in patients with classic findings, some tests can be omitted. Sometimes other tests are done. Biopsy confirms the diagnosis but is rarely necessary; demonstration of hypocomplementemia is essentially confirmatory.

Antistreptolysin O level, the most common laboratory evidence of recent streptococcal infection, increases and remains elevated for several months in about 75% of patients with pharyngitis and in about 50% of patients with impetigo, but it is not specific. An increase in antihyaluronidase and antideoxyribonuclease titers is more specific for detecting recent streptococcal skin infection but is not widely available.

Urinalysis shows proteinuria (0.5 to 2 g/m^2/day); dysmorphic RBCs; WBCs; renal tubular cells; and RBC, WBC, and granular casts. Random (spot) urinary protein/creatinine ratio may be between 0.2 and 2 (normal, < 0.2).

Serum creatinine may rise rapidly but usually peaks below a level requiring dialysis.

C3 and total hemolytic complement activity (CH50) levels fall during active disease and return to normal within 6 to 8 wk in 80% of PIGN cases; C1q, C2, and C4 levels are only minimally decreased or remain normal. Cryoglobulinemia may appear and persist for several months, whereas circulating immune complexes are detectable for only a few weeks.

Biopsy specimens show enlarged and hypercellular glomeruli, initially with neutrophilic or eosinophilic infiltration and later with mononuclear infiltration. Epithelial cell hyperplasia is a common early, transient feature. Microthrombosis may occur; if damage is severe, hemodynamic changes produce oliguria, frequently accompanied by epithelial crescents (formed within Bowman's space from epithelial cell hyperplasia). Endothelial and mesangial cells multiply, and the mesangial regions often are greatly expanded by edema and contain neutrophils, dead cells, cellular debris, and subepithelial deposits of electron-dense material. Immunofluorescence microscopy usually shows immune complex deposition with IgG and complement in a granular pattern. On electron microscopy, these deposits are semilunar or hump-shaped and are located in the subepithelial area. The presence of these deposits initiates a complement-mediated inflammatory reaction that leads to glomerular damage. Although the immune complex is presumed to contain an antigen related to streptococcal organisms, no such antigen has been found.

Prognosis

Normal renal function is retained or regained by 85 to 95% of patients. GFR usually returns to normal over 1 to 3 mo, but proteinuria may persist for 6 to 12 mo and microscopic hematuria for several years. Transient changes in urinary sediment may recur with minor URIs. Renal cellular proliferation disappears within weeks, but residual sclerosis is common. In 10% of adults and 1% of children, PIGN evolves into rapidly progressive GN.

Treatment

• Supportive care

Treatment is supportive and may include restriction of dietary protein, Na, and fluid and, in more severe cases, treatment of edema and hypertension. Dialysis is occasionally necessary. Antimicrobial therapy is preventive only when given within 36 h of infection and before GN becomes established.

Rapidly Progressive Glomerulonephritis

(Crescentic Glomerulonephritis)

Rapidly progressive glomerulonephritis (RPGN) causes microscopic glomerular crescent formation with progression to renal failure within weeks to months. Diagnosis is based on history, urinalysis, serologic tests, and renal biopsy. Treatment is with corticosteroids, with or without cyclophosphamide, and sometimes plasmapheresis.

RPGN is extensive glomerular crescent formation (which can be seen in a biopsy specimen) that, if untreated, progresses to end-stage renal disease over weeks to months. It is relatively uncommon, affecting 10 to 15% of patients with GN, and occurs predominantly in patients 20 to 50 yr. Types and causes are classified by findings using immunofluorescence microscopy (see Table 235-3).

Anti-glomerular basement membrane (GBM) antibody disease (type 1 RPGN) is autoimmune GN and accounts for up to 10% of RPGN cases. It may arise when respiratory exposures (eg, cigarette smoke, viral URI) or some other stimulus exposes alveolar capillary collagen, triggering formation of anticollagen antibodies. The anticollagen antibodies cross-react with GBM, fixing complement and triggering a cell-mediated inflammatory response in the kidneys and usually the lungs. The term Goodpasture's syndrome usually refers to a combination of GN and alveolar hemorrhage in the presence of anti-GBM antibodies (see p. 1991) but sometimes refers to GN without alveolar hemorrhage in the presence of anti-GBM antibodies. Immunofluorescent staining of renal biopsy tissue demonstrates linear IgG deposits.

Immune complex RPGN (type 2 RPGN) complicates numerous infectious and connective tissue disorders and also occurs with other primary glomerulopathies. Immunofluorescent staining demonstrates nonspecific granular immune deposits. The condition accounts for up to 40% of RPGN cases. Pathogenesis is usually unknown.

Pauci-immune RPGN (type 3 RPGN) is distinguished by the absence of immune complex or complement deposition on immunofluorescent staining. It constitutes up to 50% of all RPGN cases. Almost all patients have elevated antineutrophil cytoplasmic antibodies (ANCAs, usually myeloperoxidase-ANCA) and systemic vasculitis.

Double-antibody disease (type 4 RPGN) has features of types 1 and 3, with the presence

[**Table 235-3.** Classification of Rapidly Progressive Glomerulonephritis Based on Immunofluorescence Microscopy]

of anti-GBM and ANCA antibodies. It is rare.

Idiopathic cases are rare. They include patients with either of the following:

- Immune complexes (similar to type 2) but no obvious cause such as infection, connective tissue disorder, or glomerular disorder
- Pauci-immune features (similar to type 3) but absence of ANCA antibodies

Symptoms and Signs

Manifestations are usually insidious, with weakness, fatigue, fever, nausea and vomiting, anorexia, arthralgia, and abdominal pain. Some patients present similarly to those with PIGN, with abrupt-onset hematuria. About 50% of patients have edema and a history of an acute influenza-like illness within 4 wk of onset of renal failure, usually followed by severe oliguria. Nephrotic syndrome is present in 10 to 30%. Hypertension is uncommon and rarely severe. Patients with anti-GBM antibody disease may have pulmonary hemorrhage, which can manifest with hemoptysis or be detectable only by finding diffuse alveolar infiltrates on chest x-ray (pulmonary-renal or diffuse alveolar hemorrhage syndrome—see p. 1989).

Diagnosis

- Progressive renal failure over weeks to months
- Nephritic urinary sediment
- Serologic testing
- Renal biopsy

Diagnosis is suggested by acute renal failure in patients with hematuria and RBC casts. Testing includes serum creatinine, urinalysis, CBC, serologic tests, and renal biopsy. Diagnosis is usually by serologic tests and renal biopsy.

Serum creatinine is almost always elevated. Hematuria and RBC casts are always present, and telescopic sediment (ie, sediment with multiple elements, including WBCs and RBCs, and WBC, RBC, granular, waxy, and broad casts) is common.

On **CBC**, anemia is always present, and leukocytosis is common.

Serologic testing should include anti-GBM antibodies (anti-GBM antibody disease); antistreptolysin O antibodies, anti-DNA antibodies, or cryoglobulins (immune complex RPGN); and ANCA titers (pauci-immune RPGN). Complement measurement may be useful in suspected immune complex RPGN, because hypocomplementemia is common.

Early **renal biopsy** is essential. The feature common to all types of RPGN is focal proliferation of glomerular epithelial cells, sometimes interspersed with numerous neutrophils, that forms a crescentic cellular mass (crescents) and that fills Bowman's space in > 50% of glomeruli. The glomerular tuft usually appears hypocellular and collapses. Necrosis within the tuft or involving the crescent may occur and may be the most prominent abnormality. In such patients, histologic evidence of vasculitis should be sought.

Immunofluorescence microscopy findings differ for each type.

- In anti-GBM antibody disease (type 1), linear or ribbon-like deposition of IgG along the GBM is most prominent and is often accompanied by linear and sometimes granular deposition of C3.
- In immune complex RPGN (type 2), immunofluorescence reveals diffuse, irregular mesangial IgG and C3 deposits.
- In pauci-immune RPGN (type 3), immune staining and deposits are not detected. However, fibrin occurs

within the crescents, regardless of the fluorescence pattern.

- In double antibody RPGN (type 4), linear staining of the GBM is present (similar to type 1).

- In idiopathic RPGN some patients have immune complexes (similar to those of type 2) and others have absence of immune staining and deposits (similar to type 3).

Prognosis

Spontaneous remission is rare, and 80 to 90% of untreated patients progress to end-stage renal disease within 6 mo. Prognosis improves with early treatment.

Favorable prognostic factors include RPGN caused by the following:

- Anti-GBM disease if treated early, especially when treated before oliguria occurs and when creatinine level is < 7 mg/dL

- PIGN

- SLE

- Wegener's granulomatosis

- Polyarteritis nodosa

Unfavorable prognostic factors include the following:

- Age > 60 yr

- Oliguric renal failure

- Higher serum creatinine level

- Circumferential crescents in > 75% of glomeruli

- Among patients with pauci-immune RPGN, no response to treatment

About 30% of patients with pauci-immune RPGN do not respond to treatment; among nonresponders, about 40% require dialysis, and 33% die within 4 yr. In contrast, among patients who respond to treatment, < 20% of patients require dialysis, and about 3% die.

Patients with double-antibody disease appear to have a renal prognosis no better than patients with anti-GBM antibody disease and worse than patients with pauci-immune RPGN.

Patients who recover normal renal function after RPGN demonstrate residual histologic changes principally in glomeruli, consisting chiefly of hypercellularity, with little or no sclerosis within the glomerular tuft or the epithelial cells and minimal fibrosis of the interstitium.

Death is usually due to infectious or cardiac causes, providing that a uremic death is prevented by dialysis.

Treatment

- Corticosteroids

- Cyclophosphamide

- Plasmapheresis for anti-GBM RPGN

Treatment varies by disease type, although no regimens have been rigorously studied. Therapy should be instituted early, ideally when serum creatinine is < 5 mg/dL and before the biopsy shows crescentic involvement of all glomeruli or organizing crescents as well as fibrotic interstitium and atrophic tubules. Treatment becomes less effective as these features become more prominent and may be harmful in some patients (eg, the elderly, patients with infection).

For **anti-GBM antibody disease**, plasma-pheresis (daily 3- to 4-L exchanges for 14 days) is recommended; the role of plasmapheresis is less well defined for immune complex and pauci-immune RPGN. Plasmapheresis is believed to be effective because it rapidly removes free antibody, intact immune complexes, and mediators of inflammation (eg, fibrinogen, complement). Prednisone and cyclophosphamide are typically started and continued to minimize new antibody formation.

For **immune complex** and **pauci-immune RPGN**, corticosteroids (methylprednisolone 1 g IV once/day over 30 min for 3 to 5 days followed by prednisone 1 mg/kg po once/day) may reduce serum creatinine levels or delay dialysis for > 3 yr in 50% of patients. Cyclophosphamide 1.5 to 2 mg/kg po once/day is usually given and may particularly benefit ANCA-positive patients; monthly pulse regimens may lessen adverse effects, but their role is not defined.

Lymphocytapheresis, a technique to remove peripheral lymphocytes from circulation, may benefit pauci-immune RPGN but requires further investigation. Patients with idiopathic disease are usually treated with corticosteroids and cyclophosphamide, but data regarding efficacy are scarce.

Renal transplantation is effective for all types, but disease may recur in the graft; risk diminishes with time. In anti-GBM antibody disease, the anti-GBM titers should be undetectable for at least 12 mo before transplantation.

Thin Basement Membrane Disease

(Benign Familial Hematuria)

Thin basement membrane disease is diffuse thinning of the glomerular basement membrane from a width of 300 to 400 nm in normal subjects to 150 to 225 nm.

Thin basement membrane disease is hereditary and usually transmitted in autosomal dominant fashion. Not all genetic mutations have been characterized, but in some families with thin basement membrane disease there is a mutation in the type IV collagen α4 gene. Prevalence is estimated to be 5 to 9%.

Most patients are asymptomatic and are incidentally noted to have microscopic hematuria on routine urinalysis, although mild proteinuria and gross hematuria are occasionally present. Renal function is typically normal, but a few patients develop progressive renal failure for unknown reasons. Recurrent flank pain, similar to that in IgA nephropathy, is a rare manifestation.

Diagnosis is based on family history and findings of hematuria without other symptoms or pathology, particularly if asymptomatic family members also have hematuria. Renal biopsy is unnecessary but is often done as part of a hematuria evaluation. Early on, thin basement membrane disease may be difficult to differentiate from hereditary nephritis because of histologic similarities.

Long-term prognosis is excellent, and no treatment is necessary in most cases. Patients with frequent gross hematuria, flank pain, or proteinuria (eg, urine protein/creatinine ratio of > 0.2) may benefit from ACE inhibitors or angiotensin receptor II blockers, which may lower intraglomerular pressure.

Nephrotic Syndrome

Nephrotic syndrome is urinary excretion of > 3 g of protein/day due to a glomerular disorder. It is more common among children and has both primary and secondary causes. Diagnosis is by determination of urine protein/creatinine ratio in a random urine sample or measurement of urinary protein in a 24-h urine collection; cause is diagnosed based on history, physical

examination, serologic testing, and renal biopsy. Prognosis and treatment vary by cause.

Etiology

Nephrotic syndrome occurs at any age but is more prevalent in children, mostly between ages 1 1/2 and 4 yr. At younger ages, boys are affected more often than girls, but both are affected equally at older ages. Causes differ by age (see Table 235-1) and may be primary or secondary (see Table 235-4).

The most common primary causes are the following:

• Minimal change disease

• Focal segmental glomerulosclerosis

• Membranous nephropathy

Secondary causes account for < 10% of childhood cases but > 50% of adult cases, most commonly the following:

• Diabetic nephropathy

• Preeclampsia

Amyloidosis, an underrecognized cause, is responsible for 4% of cases.

Pathophysiology

Proteinuria occurs because of changes to capillary endothelial cells, the glomerular basement membrane (GBM), or podocytes,

[**Table 235-4.** Causes of Nephrotic Syndrome]

which normally filter serum protein selectively by size and charge.

The mechanism of damage to these structures is unknown in primary and secondary glomerular diseases, but evidence suggests that T cells may up-regulate a circulating permeability factor or down-regulate an inhibitor of permeability factor in response to unidentified immunogens and cytokines. Other possible factors include hereditary defects in proteins that are integral to the slit diaphragms of the glomeruli, activation of complement leading to damage of the glomerular epithelial cells and loss of the negatively charged groups attached to proteins of the GBM and glomerular epithelial cells.

Complications: The disorder results in urinary loss of macromolecular proteins, primarily albumin but also opsonins, immunoglobulins, erythropoietin, transferrin, hormone-binding proteins (including thyroid-binding globulin and vitamin D-binding protein), and antithrombin III. Deficiency of these and other proteins contribute to a number of complications (see Table 235-5); other physiologic factors also play a role.

Symptoms and Signs

Primary symptoms include anorexia, malaise, and frothy urine (caused by high concentrations of protein). Fluid retention may cause dyspnea (pleural effusion or laryngeal edema), arthralgia (hydrarthrosis), or abdominal pain (ascites or, in children, mesenteric edema).

Corresponding signs may develop, including peripheral edema and ascites. Edema may obscure signs of muscle wasting and cause parallel white lines in fingernail beds (Muehrcke's lines).

Other symptoms and signs are attributable to the many complications of nephrotic syndrome (see Table 235-5).

Diagnosis

• Urine protein/creatinine ratio ≥ 3 or proteinuria ≥ 3 g/24 h

• Serologic testing and renal biopsy unless the cause is clinically obvious

Diagnosis is suspected in patients with edema and proteinuria on urinalysis and confirmed by random (spot) urine protein and creatinine levels or 24-h measurement of urinary protein. The cause may be suggested by clinical findings (eg, SLE, preeclampsia, cancer); when the cause is unclear, additional (eg, serologic) testing and renal biopsy are indicated.

Urine testing: A finding of significant **proteinuria** (3 g protein in a 24-h urine collection) is diagnostic (normal excretion is < 150 mg/day). Alternatively, the protein/creatinine ratio in a random urine specimen usually reliably estimates grams of protein/1.73 m^2 BSA in a 24-h collection (eg, values of 40 mg/dL protein and 10 mg/dL creatinine in a random urine sample are equivalent to the finding of 4 g/1.73 m^2 in a 24-h specimen). Calculations based on random specimens may be less reliable when creatinine excretion is high (eg, during athletic training) or low (eg, in cachexia). However, calculations based on random specimens are usually preferred to 24-h collection because random collection is more convenient and less prone to error (eg, due to lack of adherence); more convenient

[**Table 235-5.** Complications of Nephrotic Syndrome]

testing facilitates monitoring changes that occur during treatment.

Besides proteinuria, **urinalysis** may demonstrate RBCs and casts (hyaline, granular, fatty, waxy, RBC, or epithelial cell). Lipiduria, the presence of free lipid or lipid within tubular cells (oval fat bodies), within casts (fatty casts), or as free globules, suggests a glomerular disorder causing nephrotic syndrome. Urinary cholesterol can be detected with plain microscopy and demonstrates a Maltese cross pattern under crossed polarized light; Sudan staining must be used to show triglycerides.

Adjunctive testing: Adjunctive testing helps characterize severity and complications.

• BUN and creatinine concentrations vary by degree of renal impairment.

• Serum albumin often is < 2.5 g/dL.

• Total cholesterol and triglyceride levels are typically increased.

It is not routinely necessary to measure levels of α- and γ-globulins, immunoglobulins, hormone-binding proteins, ceruloplasmin, transferrin, and complement components, but these levels may also be low.

Secondary causes: The role of testing for secondary causes (see Table 235-4) is controversial because yield may be low. Tests are best done as indicated by clinical context. Tests may include the following:

• Serum glucose or glycosylated Hb (HbA_{1c})

• Antinuclear antibodies

• Hepatitis B and C serologic tests

• Serum or urine protein electrophoresis

• Cryoglobulins

Test results may alter management and preclude the need for biopsy. For example, demonstration of cryoglobulins suggests mixed cryoglobulinemia (eg, from chronic inflammatory disorders such as SLE,

Sjogren's syndrome, or hepatitis C virus infection), and demonstration of a monoclonal protein on serum or urine protein electrophoresis suggests a monoclonal gammopathy (eg, multiple myeloma), especially in patients > 50 yr.

Renal biopsy is indicated in adults to diagnose the disorder causing idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome in children is most likely minimal change disease and is usually presumed without biopsy unless the patient fails to improve during a trial of corticosteroids. Specific biopsy findings are discussed under the individual disorders.

Prognosis

Prognosis varies by cause. Complete remissions may occur spontaneously or with treatment. The prognosis generally is favorable in corticosteroid-responsive disorders.

In all cases, prognosis may be worsened by the following:

• Infection

• Hypertension

• Significant azotemia

• Hematuria

• Thromboses in cerebral, pulmonary, peripheral, or renal veins

The recurrence rate is high in kidney transplantation patients with focal segmental glomerulosclerosis, SLE, IgA nephropathy, and membranoproliferative glomerulonephritis (especially type II).

Treatment

• Treatment of causative disorder

• Angiotensin inhibition

• Na restriction

• Statins

• Rarely, nephrectomy

Causative disorder: Treatment of underlying disorders may include prompt treatment of infections (eg, staphylococcal endocarditis, malaria, syphilis, schistosomiasis), allergic desensitization (eg, for poison oak or ivy and insect antigen exposures), and stopping drugs (eg, gold, penicillamine, NSAIDs); these measures may cure nephrotic syndrome in specific instances.

Proteinuria: Angiotensin inhibition (ACE inhibitors or angiotensin II receptor blockers) is indicated to reduce systemic and intraglomerular BP and proteinuria. These drugs may cause or exacerbate hyperkalemia in patients with moderate to severe renal insufficiency.

Protein restriction is no longer recommended because of lack of demonstrated effect on progression.

Edema: Na restriction (< 2 g Na, or about 100 mmol/day) is recommended for patients with symptomatic edema.

Loop diuretics are usually required to control edema but may worsen preexisting renal insufficiency and hypovolemia, hyperviscosity, and hypercoagulability and thus should be used only if Na restriction is ineffective.

Hyperlipidemia: Statins are indicated for hyperlipidemia.

Limitation of saturated fat and cholesterol intake is recommended to help control hyperlipidemia.

Hypercoagulability: Anticoagulants are indicated for treatment of thromboembolism, but few data exist to support their use as primary prevention.

Infection risk: All patients should receive pneumococcal vaccination if not otherwise contraindicated.

Nephrectomy: Rarely, bilateral nephrectomy is necessary in severe nephrotic syndrome because of persistent hypoalbuminemia. The same result can sometimes be achieved by embolizing the renal arteries with coils, thus avoiding surgery in high-risk patients. Renal replacement therapy is used as necessary.

Congenital Nephrotic Syndromes

Congenital and infantile nephrotic syndromes are those that manifest during the first year of life. They include diffuse mesangial sclerosis and Finnish-type nephrotic syndrome.

Diffuse mesangial sclerosis: This nephrotic syndrome is rare. Inheritance is variable. Progression to end-stage renal failure occurs by age 2 or 3 yr.

Patients with severe proteinuria may require bilateral nephrectomy because of severe hypoalbuminemia; dialysis should be initiated early to ameliorate nutritional deficits and mitigate failure to thrive. The disorder usually recurs in a renal graft.

Finnish-type nephrotic syndrome: This syndrome is an autosomal recessive disorder that affects 1/8200 Finnish neonates and is caused by a mutation in the *NPHS1* gene, which codes for a podocytic slit-diaphragm protein (nephrin).

Finnish-type nephrotic syndrome is rapidly progressive and usually necessitates dialysis within 1 yr. Most patients die within 1 yr, but a few have been supported nutritionally until renal failure occurs and then managed with dialysis or transplantation. However, the disorder may recur in a renal graft.

Other syndromes: Several other rare congenital nephrotic syndromes are now genetically characterized. These include corticosteroid-resistant nephrotic syndrome (defective *NPS2* gene coding for podocin), familial focal segmental glomerulosclerosis (defective *ACTN 4* gene coding for α-actin 4), and Denys-Drash syndrome, which is characterized by diffuse mesangial sclerosis, male pseudohermaphroditism, and Wilms' tumor (defective *WT1* gene).

Diabetic Nephropathy

(See also p. 869.)

Diabetic nephropathy (DN) is glomerular sclerosis and fibrosis caused by the metabolic and hemodynamic changes of diabetes mellitus. It manifests as slowly progressive albuminuria with worsening hypertension and renal insufficiency. Diagnosis is based on history, physical examination, urinalysis, and urine albumin/creatinine ratio. Treatment is strict glucose control, angiotensin inhibition (ACE inhibitors or angiotensin II receptor blockers), and control of BP and lipids.

DN is the most common cause of nephrotic syndrome in adults and of end-stage renal disease in the US, accounting for up to 80% of cases of the latter. The prevalence of renal failure is probably about 40% among patients with type 1 diabetes mellitus. The prevalence of renal failure among patients with type 2 diabetes mellitus is usually stated as 20 to 30%, but this figure is probably low. Renal failure is particularly common in certain ethnic groups, such as blacks, Mexican-Americans, Polynesians, and Pima Indians. Other risk factors include the following:

• Duration and degree of hyperglycemia

• Hypertension

• Dyslipidemia

• Cigarette smoking

• Certain polymorphisms affecting the reninangiotensin-aldosterone axis

• Family history of diabetic nephropathy

• Genetic variables (decreased number of glomeruli)

Renal failure usually takes ≥ 10 yr after the onset of nephropathy to develop; however, because type 2 diabetes is often present for several years before being recognized, nephropathy often develops < 10 yr after diabetes is diagnosed.

Pathophysiology

Pathogenesis begins with small vessel disease. Pathophysiology is complex, involving glycosylation of proteins, hormonally influenced cytokine release (eg, transforming growth factor-β), deposition of mesangial matrix, and alteration of glomerular hemodynamics. Hyperfiltration, an early functional abnormality, is only a relative predictor for the development of renal failure.

Hyperglycemia causes glycosylation of glomerular proteins, which may be responsible for mesangial cell proliferation and matrix expansion and vascular endothelial damage. The GBM classically becomes thickened.

Lesions of diffuse or nodular intercapillary glomerulosclerosis are distinctive. There is marked hyalinosis of afferent and efferent arterioles as well as arteriosclerosis; interstitial fibrosis and tubular atrophy may be present. Only mesangial matrix expansion appears to correlate with progression to end-stage renal disease.

DN begins as glomerular hyperfiltration (increased GFR); GFR normalizes with early renal injury and mild hypertension, which worsens over time. Microalbuminuria, urinary excretion of albumin in a range of 30 to 300 mg albumin/day, then occurs. Urinary albumin in these concentrations is called microalbuminuria because detection of proteinuria by dipstick on routine urinalysis usually requires > 300 mg albumin/day. Microalbuminuria progresses to proteinuria > 0.5 g/day at a variable course, usually over years. Nephrotic syndrome (proteinuria ≥ 3 g/day) precedes end-stage renal disease, on average, by about 3 to 5 yr, but this timing is also highly variable. Other urinary tract abnormalities commonly occurring with DN that may accelerate the decline of renal function include papillary necrosis, type IV renal tubular acidosis, and UTIs. In DN, the kidneys are usually of normal size or larger.

Symptoms and Signs

DN is asymptomatic in early stages. Sustained microalbuminuria is the earliest warning sign. Hypertension and some measure of dependent edema eventually develop in most untreated patients. In later stages, patients develop symptoms and signs of uremia (eg, nausea, vomiting, anorexia) earlier (ie, with higher GFR) than do patients without DN, possibly because the combination of end-organ damage due to diabetes (eg, neuropathy) and renal failure worsens symptoms.

Diagnosis

• Screening of all patients with diabetes with random urine albumin/creatinine ratio

• Urinalysis for signs of other renal disorders (eg, hematuria, RBC casts)

The diagnosis is suspected in patients with diabetes who have proteinuria, particularly if they have diabetic retinopathy (indicating small vessel disease) or risk factors for DN. Other renal disorders should be considered if there are any of the following:

- Heavy proteinuria with only a brief history of diabetes
- Absence of diabetic retinopathy
- Rapid onset of heavy proteinuria
- Gross hematuria
- RBC casts
- Rapid decline in GFR
- Small kidney size

Urinary protein: Patients are tested for proteinuria by routine urinalysis; if proteinuria is present, testing for microalbuminuria is unnecessary because the patient already has macroalbuminuria suggestive of diabetic renal disease. In patients without proteinuria on urinalysis, an albumin/creatinine ratio should be calculated from a mid-morning urine specimen. A ratio ≥ 0.03 mg/mg (≥ 30 mg/g) indicates microalbuminuria if it is present on at least 2 of 3 specimens within 3 to 6 mo and if it cannot be explained by infection or exercise. Some experts recommend that microalbuminuria be measured from a 24-h urine collection, but this approach is less convenient, and many patients have difficulty accurately collecting a specimen. The random urine albumin/creatinine ratio overestimates 24-h collection of microalbuminuria in up to 30% of patients > 65 due to reduced creatinine production from reduced muscle mass. Inaccurate results can also occur in very muscular patients or if vigorous exercise precedes urine collection.

For most patients with diabetes who have proteinuria, the diagnosis is clinical. Renal biopsy can confirm the diagnosis but is rarely necessary.

Screening: Patients with type 1 diabetes without known renal disease should be screened for proteinuria and, if proteinuria is absent on routine urinalysis, for microalbuminuria, beginning 5 yr after diagnosis and at least annually thereafter.

Patients with type 2 diabetes should be screened at the time of diagnosis and annually thereafter.

Prognosis

Prognosis is good for patients who are meticulously treated and monitored. Such care is often difficult in practice, however, and most patients slowly lose renal function; even prehypertension (BP 120 to 139/80 to 89 mm Hg) or stage 1 hypertension (BP 140 to 159/90 to 99 mm Hg) may accelerate injury. Systemic atherosclerotic disease (stroke, MI, peripheral arterial disease) predicts an increase in mortality.

Treatment

- Maintenance of glycosylated Hb (HbA_{1c}) ≤ 7.0
- Aggressive BP control, beginning with angiotensin inhibition

Primary treatment is strict glucose control to maintain HbA_{1c} ≤ 7.0; maintenance of euglycemia reduces microalbuminuria but may not retard disease progression once DN is well established. Glucose control must also be accompanied by strict control of BP to < 130/80 mm Hg. Some experts suggest BP should be 110 to 120/65 to 80 mm Hg, particularly in patients with protein excretion of > 1 g/day; however, others claim that BP values < 120/85 mm Hg are associated with increased cardiovascular mortality and heart failure. Dyslipidemia should also be treated.

Angiotensin inhibition is first-line therapy. Thus, ACE inhibitors or angiotensin II receptor blockers are the antihypertensives of choice; they reduce BP and proteinuria and slow the progression of DN. ACE inhibitors are usually less expensive, but angiotensin II receptor blockers can be used instead if ACE inhibitors cause persistent cough. Treatment should be started when microalbuminuria is detected regardless of whether hypertension is present; some experts recommend drugs be used even before signs of renal disease appear.

Diuretics are required by most patients in addition to angiotensin inhibition to reach target BP levels. Dose should be decreased if symptoms of orthostatic hypotension develop or serum creatinine increases by more than 30%.

Nondihydropyridine Ca channel blockers (diltiazem and verapamil) are also antiproteinuric and renoprotective and can be used if proteinuria does not meaningfully decrease when target BP is reached or as alternatives for patients with hyperkalemia or other contraindications to ACE inhibitors or angiotensin II receptor blockers. In contrast, dihydropyridine Ca channel blockers (eg, nifedipine, felodipine, amlodipine) are relatively contraindicated because they may worsen proteinuria and renal function. ACE inhibitors and nondihydropyridine Ca channel blockers have greater antiproteinuric and renoprotective effects when used together, and their antiproteinuric effect is enhanced by Na restriction. Nondihydropyridine Ca channel blockers should be used with caution in patients taking β-blockers.

Dietary protein restriction yields mixed results. The American Diabetic Association recommends that people with diabetes and overt nephropathy be restricted to 0.8 g protein/kg/day. Significant protein restriction should be done only with close dietary monitoring to ensure a balanced supply of amino acids, because undernutrition may be a significant risk.

Kidney transplantation with or without simultaneous or subsequent pancreas transplantation (see p. 1133) is an option for patients with end-stage renal disease. The 5-yr survival rate for patients with type 2 diabetes receiving a kidney transplant is almost 60%, compared with 2% for dialysis-dependent patients who do not undergo transplantation (though this statistic probably represents significant selection bias). Renal allograft survival rate is > 85% at 2 yr.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is scattered (segmental) mesangial sclerosis in some but not all (focal) glomeruli. It is most often idiopathic but may be secondary to use of heroin or other drugs, HIV infection, obesity, sickle cell disease, atheroembolic disease, or nephron loss (eg, in reflux nephropathy or subtotal nephrectomy). It manifests mainly in adolescents but also in young and middle-aged adults. Patients have insidious onset of proteinuria, mild hematuria, hypertension, and azotemia. Diagnosis is confirmed by renal biopsy. Treatment is with angiotensin inhibition and, for idiopathic disease, corticosteroids and sometimes cytotoxic drugs.

FSGS is now the most common cause of idiopathic (or primary) nephrotic syndrome among adults in the US. It is especially common in black men. Though usually idiopathic, FSGS can occur in association with other factors (secondary FSGS), including drugs (eg, heroin, interferon alfa, pamidronate, cyclosporine, or acetaminophen or NSAIDs [causing analgesic nephropathy]), atheroembolic disease affecting the kidneys, obesity, HIV infection (see p. 2404), and disorders causing nephron loss (eg, reflux nephropathy, subtotal nephrectomy, renal dysgenesis). Familial cases exist.

In FSGS, because charge as well as size ultrafiltration barriers are defective, proteinuria is typically nonselective, affecting high molecular-weight proteins (eg, Igs) as well as albumin. Kidneys tend to be small.

Symptoms and Signs

FSGS patients commonly present with heavy proteinuria, hypertension, renal dysfunction, edema, or a combination; however, asymptomatic, non-nephrotic-range proteinuria is sometimes the only sign.

Microscopic hematuria is occasionally present.

Diagnosis

• Renal biopsy, when possible, with immunostaining and electron microscopy

FSGS is suspected in patients with nephrotic syndrome, proteinuria, or renal dysfunction with no obvious cause, particularly patients who have disorders or use drugs associated with FSGS.

Urinalysis is done and BUN, serum creatinine, and 24-h urinary protein excretion are measured. Diagnosis is confirmed by renal biopsy, which shows focal and segmental hyalinization of the glomeruli, often with immunostaining showing IgM and complement (C3) deposits in a nodular and coarse granular pattern. Electron microscopy reveals diffuse effacement of podocyte foot processes. Global sclerosis may be visible, along with secondary atrophic glomeruli. Biopsy may be falsely negative if areas of focal abnormalities are not sampled.

Prognosis

Prognosis is poor. Spontaneous remissions occur in < 10% of patients. Renal failure occurs in > 50% of patients within 10 yr; in 20%, end-stage renal disease occurs within 2 yr despite treatment. The disorder is more rapidly progressive in adults than in children. The presence of segmental sclerosis consistently at the glomerular pole where the tubule originates (tip lesion) may portend a more favorable response to corticosteroid therapy. Another variant, in which the capillary walls are wrinkled or collapsed (collapsing glomerulopathy, which is typical in association with IV drug abuse or HIV infection), suggests more severe disease and rapid progression to renal failure. Pregnancy may exacerbate FSGS.

FSGS may recur after renal transplantation; proteinuria sometimes returns within hours of transplantation. Of patients whose transplant was for end-stage renal disease caused by FSGS, about 8 to 20% lose their graft due to recurrent FSGS; risk is highest in young children, patients who develop renal failure < 3 yr after disease onset, and patients with mesangial proliferation.

Heroin addicts with nephrotic syndrome due to FSGS can experience complete remission if they cease taking heroin early in the disease.

Treatment

• Angiotensin inhibition

• Corticosteroids and sometimes cytotoxic drugs for idiopathic FSGS

Treatment often is not effective. Patients with FSGS should be treated with angiotensin inhibition (an ACE inhibitor or an angiotensin II receptor blocker) unless contraindicated by angioedema or hyperkalemia. Patients with nephrotic syndrome should be treated with a statin. In patients with secondary FSGS, the primary disorder should be treated. A trial of immunosuppressive therapy is indicated in idiopathic FSGS if proteinuria reaches the nephrotic range or if any degree of renal dysfunction is present.

Immunosuppressive therapy: Corticosteroids (eg, prednisone 1 mg/kg po once/day or 2 mg/kg every other day) are recommended for at least 2 mo, although some experts recommend use for up to 9 mo. Response rates of 30 to 50% have been reported with prolonged therapy. After a 2-wk remission of proteinuria, the corticosteroid is slowly tapered over ≥ 2 mo. Secondary and familial cases are more likely to be corticosteroid-resistant.

If only slight improvement or relapse occurs with corticosteroid therapy, cyclosporine (1.5 to 2 mg/kg po bid for 6 mo) or, alternatively, mycophenolate mofetil (750 to 1000 mg po bid for 6 mo in patients > 1.25 m^2 BSA or 600 mg/m^2 BSA bid up to 1000 mg bid) may induce remission. In patients with contraindications to high-dose corticosteroids (eg, diabetes, osteoporosis), cyclosporine can be given along with a lower dose of corticosteroids (eg, prednisone 0.15 mg/kg po once/day). An alternative is plasmapheresis with tacrolimus immunosuppression.

HIV-Associated Nephropathy

HIV-associated nephropathy (HIVAN) is characterized by clinical findings similar to those of focal segmental glomerulosclerosis and often biopsy features of collapsing glomerulopathy (a variant of focal segmental glomerulosclerosis).

HIVAN seems to be more common among black patients with HIV who are injection drug users. Infection of renal cells with HIV may contribute.

Most clinical findings are similar to those of FSGS, but hypertension is less common and the kidneys remain enlarged. Most patients experience rapid progression to end-stage renal disease within 1 to 4 mo.

Diagnosis

• Renal biopsy

HIVAN is suspected in patients with nephrotic syndrome or nephropathy who have AIDS or symptoms of AIDS. HIVAN should be distinguished from the many other disorders that occur with higher frequency in HIV-infected patients and cause renal disease, such as thrombotic microangiopathy (hemolyticuremic syndrome and thrombotic thrombocytopenic purpura), immune complex-mediated glomerulonephritis, and drug-induced interstitial nephritis (due to indinavir and ritonavir) and rhabdomyolysis (due to statins).

In HIVAN, ultrasonography, if done, shows that the kidneys are enlarged and highly echogenic. Renal biopsy typically is done. Light microscopy shows capillary collapse of varying severity (collapsing glomerulopathy) and differing degrees of increased mesangial matrix. Tubular cells show marked degenerative changes and tubular atrophy or microcytic dilation. Interstitial immune cell infiltrate, fibrosis, and edema are common. Tubular reticular inclusions, similar to those in SLE, are found within endothelial cells but are now rare with more effective HIV therapy. Normotension and persistently enlarged kidneys help to differentiate HIVAN from FSGS.

Treatment

• Antiretroviral therapy and ACE inhibitors

Control of the HIV infection may help minimize renal damage. ACE inhibitors are probably of some benefit. The role of corticosteroids is not well defined. Dialysis is usually required. At some centers, outcomes after transplantation have been excellent.

Membranous Nephropathy

Membranous nephropathy (MN) is deposition of immune complexes on the GBM with GBM thickening. Cause is usually unknown, altions, autoimmune disorders, and cancer. Manifestations include insidious onset of edema and heavy proteinuria with benign urinary sediment, normal renal function, and normal or elevated BP. Diagnosis is by renal biopsy. Spontaneous remission is common. Treatment of patients at high risk of progression is usually with corticosteroids and cyclophosphamide or chlorambucil.

MN mostly affects adults, in whom it is a common cause of nephrotic syndrome.

Etiology

MN is usually idiopathic but may be secondary to any of the following:

• Drugs (eg, gold, penicillamine, NSAIDs)

• Infections (eg, hepatitis B virus infection, syphilis)

• Autoimmune disorders (eg, SLE)

• Thyroiditis

• Cancer

• Parasitic diseases (eg, malaria, schistosomiasis, leishmaniasis)

Depending on the patient's age, 4 to 20% have an underlying cancer, including solid cancers of the lung, colon, stomach, breast, or kidney; Hodgkin or non-Hodgkin lymphoma; chronic lymphocytic leukemia; and melanoma.

MN is rare in children and, when it occurs, is usually due to hepatitis B virus infection or SLE.

Renal vein thrombosis is especially frequent in MN but is usually clinically silent unless it progresses to pulmonary embolism.

Symptoms and Signs

Patients typically present with edema and nephrotic-range proteinuria and occasionally with microscopic hematuria and hypertension. Symptoms and signs of a disorder causing MN (eg, a cancer) may be present initially.

Diagnosis

• Renal biopsy

• Evaluation for secondary causes

Diagnosis is suggested by development of nephrotic syndrome, particularly in patients who have potential causes of MN. The diagnosis is confirmed by biopsy.

Proteinuria is in the nephrotic range in 80%. Laboratory testing is done as indicated for nephrotic syndrome. The GFR, if measured, is normal or decreased. Immune complexes are seen as dense deposits on electron microscopy (see Fig. 235-1). Subepithelial dense deposits occur with early disease, with spikes of lamina densa between the deposits. Later, deposits appear within the GBM, and marked thickening occurs. A diffuse, granular pattern of IgG deposition occurs along the GBM without cellular proliferation, exudation, or necrosis.

Evaluation of patients diagnosed with MN usually includes the following:

• A search for occult cancer, particularly in a patient who has lost weight, has unexplained anemia or heme-positive stools, or is elderly

• Consideration of drug-induced MN

• Hepatitis B and C serologic testing

• Antinuclear antibody testing

The search for occult cancer is usually limited to age-appropriate screening (eg, colonoscopy for patients age > 50 or with other symptoms or risk factors, mammogram for women age > 40, prostate-specific antigen measurement for men age > 50 [age > 40 for blacks], chest x-ray and possibly chest CT for patients at risk of lung cancer).

Prognosis

About 25% of patients undergo spontaneous remission, 25% develop persistent, nonnephrotic-range

proteinuria, 25% develop persistent nephrotic syndrome, and 25% progress to end-stage renal disease. Women, children, and young adults with non-nephrotic-range proteinuria and patients with persistently normal renal function 3 yr after diagnosis tend to have little disease progression. More than 50% of patients with nephrotic-range proteinuria who are asymptomatic or who have edema that can be controlled with diuretics will have a partial or complete remission within 3 to 4 yr.

Risk of progression to renal failure is highest among patients with

• Proteinuria ≥ 10 g/day, particularly men age > 50 yr

• An elevated serum creatinine level at presentation or diagnosis

• Biopsy evidence of substantial interstitial inflammation

Treatment

• Treatment of secondary causes and of nephrotic syndrome as indicated

• Immunosuppressive therapy for patients at high risk of progression

Primary treatment is that of the causes. Among patients with idiopathic MN, asymptomatic patients with non-nephrotic-range proteinuria do not require treatment; renal function should be monitored periodically (eg, twice yearly when apparently stable). Patients with nephrotic-range proteinuria who are asymptomatic or who have edema that can be controlled with diuretics should be treated for nephrotic syndrome. Patients with hypertension should be given an ACE inhibitor or angiotensin II receptor blocker; these drugs may also benefit patients without hypertension by reducing proteinuria.

Immunosuppressive therapy: Immuno suppressants should be considered only for patients with symptomatic idiopathic nephrotic syndrome and for those most at risk of progressive disease. Older and chronically ill patients are at greater risk of infectious complications from immunosuppressants. No consensus protocol exists, but one approach

[Fig. 235-1. Electron microscopic features in immunologic glomerular disorders.]

uses methylprednisolone 1 g IV for 3 days, after which prednisone 0.5 mg/kg po once/day is given for the next 27 days. The following month, chlorambucil 0.1 to 0.2 mg/kg po once/day is given for 1 mo. These 2 monthly regimens are alternated for a total of 6 mo. This protocol remains controversial and should be used with caution, especially in the elderly because of the increased risk of infection. Some experts favor use of combinations of cyclophosphamide and corticosteroids because of their better safety profile.

For patients who are intolerant of cytotoxic drugs or who do not respond to them, cyclosporine 4 to 6 mg/kg po once/day for 4 mo may be beneficial. Therapies of unproven long-term value include IV immune globulin and NSAIDs.

Minimal Change Disease

(Lipoid Nephrosis; Nil Disease)

Minimal change disease (MCD) causes abrupt onset of edema and heavy proteinuria, mostly in children. Renal function is typically normal. Diagnosis is based on clinical findings or renal biopsy. Prognosis is excellent. Treatment is with corticosteroids or, in patients who do not respond, cyclophosphamide or cyclosporine.

MCD is the most common cause of nephrotic syndrome in children 4 to 8 yr (80 to 90% of childhood nephrotic syndrome), but it also occurs in adults (10 to 20% of adult nephrotic syndrome). The cause is almost always unknown, although rare cases may occur secondary to drug use (especially NSAIDs) and hematologic cancers (especially Hodgkin lymphoma).

MCD causes nephrotic syndrome, usually without hypertension or azotemia; microscopic hematuria occurs in about 20% of patients, mainly adults. Azotemia can occur in secondary cases and in patients > 60 yr. Albumin is lost in the urine of patients with MCD more so than larger serum proteins probably because MCD causes changes in the charge barrier that affect albumin selectively.

Diagnosis

• Renal biopsy in adults with idiopathic nephrotic syndrome

In children, the following:

• Sudden onset of unexplained nephrotic-range proteinuria that is mainly albumin

• Normal renal function

• Non-nephritic urine sediment

• Renal biopsy in atypical cases

Renal biopsy is required in atypical cases and in adults. Electron microscopy demonstrates edema with diffuse swelling (effacement) of foot processes of the epithelial podocytes (see Fig. 235-1). Complement and Ig deposits are absent on immunofluorescence. Although effacement is not observed in the absence of proteinuria, heavy proteinuria may occur with normal foot processes.

Treatment

• Corticosteroids

• Sometimes cyclophosphamide or cyclosporine

Spontaneous remissions occur in 40% of cases, but most patients are given corticosteroids. About 80 to 90% of patients respond to initial corticosteroid therapy (eg, prednisone 60 mg/m^2 po once/day for 4 to 6 wk in children and 1 to 1.5 mg/kg po once/day for 6 to 8 wk in adults), but 40 to 60% of responders relapse. Patients who respond (ie, have cessation of proteinuria or a diuresis if edema is present) should continue prednisone for another 2 wk and change to a maintenance regimen to minimize toxicity (2 to 3 mg/kg on alternate days for 4 to 6 wk in children and for 8 to 12 wk in adults, tapering during the next 4 mo). More prolonged initial therapy and slower tapering of prednisone lower relapse rates. Nonresponsiveness may be due to underlying focal sclerosis that was missed on biopsy due to sampling error.

In corticosteroid nonresponders (< 5% of children and > 10% of adults), frequent relapsers, and corticosteroid-dependent patients, prolonged remission may be achieved with an oral cytotoxic drug (usually cyclophosphamide 2 to 3 mg/kg once/day for 12 wk or chlorambucil 0.15 mg/kg once/day for 8 wk). However, these drugs may suppress gonadal function (most serious in prepubertal adolescents), cause hemorrhagic cystitis, have mutagenic potential, and suppress bone marrow and lymphocyte function. Dosage should be monitored with frequent CBCs, and hemorrhagic cystitis should be sought by urinalysis. Adults, particularly if older or hypertensive, are more prone to adverse effects from these cytotoxic drugs. Another alternative is cyclosporine 3 mg/kg po bid, adjusted to obtain a whole-blood trough concentration of 50 to 150 µg/L (40 to 125 nmol/L).

Complete remission occurs in > 80% of patients treated with corticosteroids, and treatment is usually continued for 1 to 2 yr. However, half or more relapse, requiring treatment with the same or a different regimen. Patients responsive to cyclosporine frequently relapse when the drug is stopped.

Most patients who are unresponsive to these interventions respond to alternative therapies, including ACE inhibitors, thioguanine, levamisole, azathioprine, and mycophenolate mofetil; < 5% progress to renal failure.

Nephritic and Nephrotic Syndromes

Several glomerular disorders typically manifest with features of both nephritic and nephrotic syndromes. These disorders include fibrillary and immunotactoid glomerulopathies, membranoproliferative glomerulonephritis (GN), and lupus nephritis.

Fibrillary and Immunotactoid Glomerulopathies

Fibrillary and immunotactoid glomerulopathies are rare conditions defined pathologically by organized deposition of nonamyloid microfibrillar or microtubular structures within the renal mesangium and basement membrane.

Fibrillary and immunotactoid glomerulopathies are thought by some experts to be related disorders. They are found in about 0.6% of renal biopsy specimens, occur equally in men and women, and have been described in patients ≥ 10 yr. Average age at diagnosis is about 45. Mechanism is unknown, although deposition of immunoglobulin, particularly IgG κ and λ light chains and complement (C3), suggests immune system dysfunction. Patients may have accompanying paraproteinemia, cryoglobulinemia, plasma cell dyscrasia, hepatitis C infection, or SLE, or they may have a primary renal disease without evidence of systemic disease.

All patients have proteinuria, > 60% in the nephrotic range. Microscopic hematuria is present in about 60%; hypertension, in about 70%. Slightly > 50% have renal insufficiency at presentation.

Diagnosis

• Renal biopsy

Diagnosis is suggested by laboratory data and confirmed by renal biopsy. If nephrotic syndrome is present, testing is done as for other cases of nephrotic syndrome. Urinalysis usually shows features of nephritic and nephrotic syndromes. Serum C3 and C4 are usually measured and are occasionally decreased. Light microscopy of a biopsy specimen shows mesangial expansion by amorphous eosinophilic deposits and mild mesangial hypercellularity. Various other changes may be present on light microscopy (eg, crescent formation, membranoproliferative patterns). Congo red staining is negative for amyloid. Immunostaining reveals IgG and C3 and sometimes κ and λ light chains in the area of the deposits. Electron microscopy shows glomerular deposits consisting of extracellular, elongated, non-branching microfibrils or microtubules. The diameter of the microfibrils and microtubules varies from 9 nm to > 50 nm. Some experts distinguish immunotactoid from fibrillary glomerulopathy by the presence of microtubular (as opposed to smaller microfibrillar) structures in the deposits; others distinguish them by the presence of a related systemic illness such as a paraproteinemia, cryoglobulinemia, or SLE in immunotactoid GN.

Prognosis

The condition is usually slowly progressive with renal insufficiency, progressing to end-stage renal disease in 50% of patients within 2 to 4 yr. A more rapid decline is predicted within the presence of hypertension, nephrotic-range proteinuria, and renal insufficiency at presentation.

Treatment

Evidence to support specific treatments is lacking. Immunosuppressants have been used based on anecdotal evidence; success may be greater with corticosteroids when serum complement is decreased.

Membranoproliferative Glomerulonephritis

(Mesangiocapillary Glomerulonephritis; Lobular Glomerulonephritis)

Membranoproliferative GN is a heterogeneous group of disorders that share mixed nephritic and nephrotic features and microscopic findings. They mostly affect children. Cause is immune

complex deposition that is idiopathic or secondary to a systemic disorder. Diagnosis is by renal biopsy. Prognosis is generally poor. Treatment, when indicated, is with corticosteroids and antiplatelet drugs.

Membranoproliferative GN is a group of immune-mediated disorders characterized histologically by glomerular basement membrane (GBM) thickening and proliferative changes on light microscopy. There are 3 types, each of which may have primary (idiopathic) or secondary causes. Primary forms affect children and young adults between ages 8 and 30 and account for 10% of cases of nephrotic syndrome in children; secondary causes tend to affect adults > 30. Men and women are affected equally. Reported familial cases of some types suggest genetic factors play a role in at least some cases. Many factors contribute to hypocomplementemia.

Type I (mesangial proliferation with immune deposits) accounts for 80 to 85% of cases. The idiopathic form is rare. Type I most commonly occurs secondary to one of the following:

- Systemic immune complex disorder (eg, SLE, mixed cryoglobulinemia, Sjogren's syndrome)
- Chronic infection (eg, bacterial endocarditis, HIV infection, hepatitis B or C infection, visceral abscess, ventriculoatrial shunt infection)
- Cancer (eg, chronic lymphocytic leukemia, lymphomas, melanoma)
- Other disorders (eg, partial lipodystrophy, C2 or C3 deficiencies, sarcoidosis, thrombotic microangiopathies)

Type II (similar to type I with less mesangial proliferation and with GBM dense deposits) accounts for 15 to 20%. It is probably an autoimmune disorder in which an IgG autoantibody (C3 nephritic factor) binds C3 convertase, rendering C3 resistant to inactivation; immunofluorescent staining identifies C3 around dense deposits and in mesangium.

Type III is thought to be a disorder similar to type I and accounts for few cases. Cause is unknown but may be related to immune complex (IgG, C3) deposition. An IgG autoantibody against the terminal component of complement is found in 70% of patients. Subepithelial deposits can occur focally and appear to disrupt the GBM.

Symptoms and Signs

Symptoms and signs are those of nephrotic syndrome in 60 to 80% of cases. Symptoms and signs of nephritic syndrome (acute GN) are presenting features in 15 to 20% of cases of type I and III disease and in a higher percentage of type II disease. At diagnosis, 30% of patients have hypertension and 20% have renal insufficiency; hypertension often develops even before GFR declines. Patients with type II disease have a greater incidence of ocular abnormalities (basal laminar drusen, diffuse retinal pigment alterations, diskiform macular detachment, choroidal neovascularization), which ultimately impair vision.

Diagnosis

- Renal biopsy
- Serum complement profile
- Serologic tests

Diagnosis is confirmed by renal biopsy, but other tests are done.

Serum complement profiles are more frequently abnormal in membranoproliferative GN than in other glomerular disorders and provide supportive evidence of the diagnosis. C3 levels are often low. In type I disease, C3 is depressed more often than C4 at diagnosis and decreases further during follow-up, but eventually normalizes. In type II disease, C3 is more frequently and severely reduced. In type III disease,

C3 is reduced but C4 is normal. C3 nephritic factor is detectable in 80% of patients with type II and in some patients with type I disease. Terminal complement nephritic factor is detectable in 20% of patients with type I, rare patients with type II, and 70% of patients with type III disease.

Serologic tests (eg, for SLE, hepatitis B and C virus, and cryoglobulinemia) are warranted to check for secondary causes of type I disease.

CBC, often obtained in the course of diagnostic evaluation, demonstrates normochromicnormocytic anemia, often out of proportion to the stage of renal insufficiency (possibly because of hemolysis), and thrombocytopenia from platelet consumption.

Prognosis

Prognosis is good if a condition causing secondary membranoproliferative GN is successfully treated. Idiopathic type I membranoproliferative GN often progresses slowly; type II progresses more rapidly. In general, the long-term prognosis is poor. End-stage renal disease occurs in 50% of patients at 10 yr and in 90% at 20 yr. Spontaneous remission occurs in < 5% with type II. Type I membranoproliferative GN recurs in 30% of kidney transplantation patients; type II recurs in 90%. Outcome tends to be worse if proteinuria is in the nephrotic range.

Treatment

• Corticosteroids for children with nephrotic-range proteinuria

• Dipyridamole and aspirin for adults

Underlying disorders are treated when possible. Specific therapy is probably not indicated in patients with non-nephrotic-range proteinuria because the disorder usually progresses slowly.

Among children with nephrotic-range proteinuria, treatment with corticosteroids, eg, prednisone 2.5 mg/kg po once/day on alternate days (maximum 80 mg/day) for 1 yr, followed by tapering to a maintenance dose of 20 mg on alternate days for 3 to 10 yr, may stabilize renal function. However, corticosteroid treatment may retard growth and cause hypertension.

Among adults, dipyridamole (225 mg po once/day) with aspirin (975 mg po once/day) for 1 yr may stabilize renal function at 3 to 5 yr, but at 10 yr there is no difference from placebo. Studies of antiplatelet therapy yield inconsistent results.

Alternate therapies are sometimes substituted for the usual treatments (eg, corticosteroids could exacerbate underlying hepatitis C). Alternative therapies include pegylated interferon alfa 2A or 2B (with addition of ribavirin if creatinine clearance is > 50 mL/min) for hepatitis C virus-associated disease and plasmapheresis with corticosteroids for concomitant severe cryoglobulinemia or rapidly progressive GN. ACE inhibitors may decrease proteinuria and help control hypertension.

Lupus Nephritis

Lupus nephritis is GN caused by SLE. Clinical findings include hematuria, nephrotic-range proteinuria, and, in advanced stages, azotemia. Diagnosis is based on renal biopsy. Treatment is of the underlying disorder and usually involves corticosteroids and cytotoxic or other immunosuppressant drugs.

Lupus nephritis is diagnosed in about 50% of SLE patients (see p. 305) and typically develops within 1 yr of diagnosis. However, the total incidence is probably > 90%, because renal biopsy in patients with suspected SLE without clinical evidence of renal disease shows changes of GN.

Pathophysiology

Pathophysiology involves immune complex deposition with development of GN. The immune complexes

consist of nuclear antigens (especially DNA), high-affinity complement-fixing IgG antinuclear antibodies, and antibodies to DNA. Subendothelial, intramembranous, subepithelial, or mesangial deposits are characteristic. Wherever immune complexes are deposited, immunofluorescence staining is positive for complement and for IgG, IgA, and IgM in varying proportions. Epithelial cells may proliferate, forming crescents. Classification of lupus nephritis is based on histologic findings (see Table 235-6).

Antiphospholipid syndrome nephropathy: This syndrome may occur with or without lupus nephritis in up to one third of patients with SLE. In the antiphospholipid antibody syndrome, circulating lupus anticoagulant (see p. 975) causes microthrombi, endothelial damage, and cortical ischemic atrophy. Antiphospholipid syndrome nephropathy increases a patient's risk of hypertension and renal insufficiency or failure compared with lupus nephritis alone.

Symptom and Signs

The most prominent symptoms and signs are those of SLE; patients who present with renal disease may have edema, foaming urine, hypertension, or a combination.

Diagnosis

• Urinalysis and serum creatinine (all patients with SLE)

• Renal biopsy

Diagnosis is suspected in all patients with SLE, particularly in patients who have proteinuria, microscopic hematuria, RBC casts, or hypertension. Diagnosis is also suspected in patients with unexplained hypertension, elevated serum creatinine levels, or abnormalities on urinalysis who have clinical features suggesting SLE.

Urinalysis is done and serum creatinine is measured. If either is abnormal, renal biopsy is usually done to confirm the diagnosis and classify the disorder histologically. Histologic

[**Table 235-6.** Classification of Lupus Nephritis]

classification helps determine prognosis and direct treatment.

Some of the histologic subtypes are similar to other glomerulopathies; eg, membranous and diffuse proliferative lupus nephritis are histologically similar to idiopathic membranous GN and type I membranoproliferative GN, respectively. Overlap between these categories is substantial, and patients may progress from one class to another over time.

Renal function and SLE activity should be monitored regularly. A rising serum creatinine level reflects deteriorating renal function, while a falling serum complement level or a rising anti-DNA antibody titer suggests increased disease activity.

Prognosis

Class of nephritis influences renal prognosis (see Table 235-6), as do other renal histologic features. Renal biopsies are scored with a semiquantitative activity score and with a chronicity index.

The **activity score** describes the degree of inflammation. The score is based on cellular proliferation, fibrinoid necrosis, cellular crescents, hyaline thrombi, wire loop lesions, glomerular leukocyte infiltration, and interstitial mononuclear cell infiltration.

The **chronicity index** describes the degree of scarring. It is based on presence of glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. The chronicity index predicts progression of lupus nephritis to renal failure. A mild to moderate chronicity score suggests at least partially reversible disease, whereas more severe chronicity scores may indicate irreversible disease. The activity score is

less well correlated with disease progression, perhaps because it is based on the degree of inflammation, which is more reversible with treatment.

Patients with lupus nephritis are at high risk of cancers, primarily B-cell lymphomas. Risk of atherosclerotic complications (eg, coronary artery disease, ischemic stroke) is also high, because of frequent vasculitis, hypertension, hyperlipidemia, and use of corticosteroids.

Treatment

• Angiotensin inhibition for hypertension or proteinuria

• Cyclophosphamide and prednisone for active, potentially reversible nephritis

Immunosuppression: Treatment is toxic and thus is reserved for nephritis that has the following characteristics:

• Is active

• Has the potential for a poor prognosis

• Is potentially reversible

Activity is estimated by the activity score as well as clinical criteria (eg, urine sediment, increasing urine protein, increasing serum creatinine). Many experts believe that a mild to moderate chronicity score, because it suggests reversibility, should provoke more aggressive therapy than a more severe chronicity score. Nephritis with the potential for deterioration and for reversibility is usually class III or IV; it is unclear whether class V nephritis warrants aggressive treatment.

Treatment usually combines cytotoxic drugs, corticosteroids, and sometimes other immunosuppressants. Induction is with cyclophosphamide, which is usually given in IV boluses (monthly for up to 6 mo) beginning with 0.75 g/m^2 in a saline solution over 30 to 60 min and, assuming a WBC count > 3000/µL, increasing to a maximum of 1 g/m^2. Oral or IV fluid administration to create rapid urine flow minimizes the bladder toxicity of cyclophosphamide, as does mesna (see p. 308). Prednisone is begun at 60 to 80 mg po once/day and tapered according to response to 20 to 25 mg every other day over 6 to 12 mo. The amount of prednisone is determined by the extrarenal manifestations and number of relapses. Relapses are usually treated with increasing doses of prednisone.

Many experts are replacing the more toxic cyclophosphamide maintenance regimens (after induction with 6 or 7 monthly IV cyclophosphamide doses) with protocols using mycophenolate mofetil (500 mg to 1 g po bid) or azathioprine (2 mg/kg po once/day, maximum 150 to 200 mg/day). Chlorambucil, cyclosporine, and tacrolimus have also been used, but relative efficacies are not clear. Low-dose prednisone (0.05 to 0.2 mg/kg po once/day) is continued and titrated based on disease activity. Duration of maintenance therapy is at least 1 yr.

Other treatments: Angiotensin inhibition with an ACE inhibitor or angiotensin II receptor blocker is indicated for patients with even mild hypertension (eg, BP > 130/80 mm Hg) or proteinuria. Also, hyperlipidemia and risk factors for atherosclerosis should be treated aggressively.

Anticoagulation is of theoretical benefit for patients with antiphospholipid syndrome nephropathy, but the value of such treatment has not been established.

Chapter 236. Tubulointerstitial Diseases

Introduction

Tubulointerstitial diseases are clinically heterogeneous disorders that share similar features of tubular and interstitial injury. In severe and prolonged cases, the entire kidney may become involved, with glomerular dysfunction and even renal failure. The primary categories of tubulointerstitial disease are acute tubular necrosis and acute or chronic tubulointerstitial nephritis.

Pathophysiology

The kidneys are exposed to unusually high concentrations of toxins. The kidneys have the highest blood supply of all tissues (about 3.5 mL/g/min), and unbound solutes leave the circulation via glomerular filtration at ≥ 100 mL/min; as a result, toxic agents are delivered at a rate 50 times that of other tissues and in much higher concentrations. When urine is concentrated, the luminal surfaces of tubular cells may be exposed to molecule concentrations 300 to 1000 times greater than those of plasma. The fine brush border of proximal tubular cells exposes an enormous surface area. A countercurrent flow mechanism increases ionic concentration of the interstitial fluid of the medulla (and thereby increases urine concentration) up to 4 times the plasma concentration.

In addition, factors can affect cellular vulnerability after exposure to toxins. Tubular transport mechanisms separate drugs from their binding proteins, which normally protect cells from toxicity. Transcellular transport exposes the interior of the cell and its organelles to newly encountered chemicals. Binding sites of some agents (eg, sulfhydryl groups) may facilitate entry but retard exit (eg, heavy metals). Chemical reactions (eg, alkalinization, acidification) may alter transport in either direction. Blockade of transport receptors may alter tissue exposure (eg, diuresis from blockade of adenosine A1 receptors may decrease exposure). Finally, the kidneys have the highest O_2 and glucose consumption per gram of tissue and are therefore vulnerable to toxins affecting cell energy metabolism.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is kidney injury characterized by acute tubular cell injury and dysfunction. Common causes are hypotension causing renal hypoperfusion and nephrotoxic drugs. The condition is asymptomatic unless it causes renal failure. The diagnosis is suspected when azotemia develops after a hypotensive event, severe sepsis, or drug exposure and is distinguished from prerenal azotemia by laboratory testing and response to volume expansion. Treatment is supportive.

Causes of ATN include the following:

• Hypotension (ischemic ATN; common)

• Nephrotoxins (common)

• Sepsis (common)

• Major surgery

• Third-degree burns covering > 15% of BSA

• The heme pigments myoglobin and hemoglobin (uncommon)

• Disorders resulting in other endogenous toxins, such as tumor lysis or multiple myeloma (uncommon)

• Poisons, such as ethylene glycol (uncommon)

• Herbal and folk remedies, such as ingestion of fish gallbladder in Southeast Asia (uncommon)

Common nephrotoxins include the following:

• Aminoglycosides

• Amphotericin B

• Cisplatin

• Radiocontrast (particularly agents with osmolality > 100 mL)

• NSAIDs

Massive volume loss, particularly in patients with septic or hemorrhagic shock or pancreatitis or in patients who have had serious surgery, increases the risk of ischemic ATN; patients with serious comorbidities are at highest risk. Serious surgery and advanced hepatobiliary disease, poor perfusion states, and advanced age increase the risk of aminoglycoside toxicity. Certain drug combinations (eg, aminoglycosides with amphotericin B) may be especially nephrotoxic. NSAIDs may cause several types of intrinsic kidney disease, including ATN. Toxic exposures cause patchy, segmental, tubular luminal occlusion with casts and cellular debris or segmental tubular necrosis.

ATN is more likely to develop in patients with the following:

• Baseline creatinine clearance < 47 mL/min

• Diabetes mellitus

• Preexisting hypovolemia or poor renal perfusion

Symptoms and Signs

ATN is usually asymptomatic but may cause symptoms or signs of acute renal failure, typically oliguria (see p. 2252) initially.

Diagnosis

• Differentiation from prerenal azotemia, based mainly on laboratory findings and, in the case of blood or fluid loss, response to volume expansion

ATN is suspected when serum creatinine rises ≥ 0.5 mg/dL/day above baseline after an apparent trigger (eg, hypotensive event, exposure to a nephrotoxin); the rise in creatinine may occur days after exposure to some nephrotoxins. ATN must be differentiated from prerenal azotemia because treatment differs. In prerenal azotemia, renal perfusion is decreased enough to elevate serum BUN out of proportion to creatinine, but not enough to cause ischemic damage to tubular cells. Prerenal azotemia can be caused by direct intravascular fluid loss (eg, from hemorrhage, GI tract or urinary losses) or by a relative decrease in effective circulating volume *without* loss of total body fluid (eg, in heart failure, portal hypertension with ascites). If fluid loss is the cause, volume expansion using IV normal saline solution normalizes serum creatinine level. If ATN is the cause, IV saline typically causes no rapid change in serum creatinine.

Laboratory findings also help distinguish ATN from prerenal azotemia (see Table 236-1).

Prognosis

In otherwise healthy patients, prognosis is good when the underlying insult is corrected; serum creatinine typically returns to normal or near-normal within 1 to 3 wk. In sick patients, even when acute renal failure is mild, morbidity and mortality are increased. Prognosis is better in patients who do not require ICU care

(32% mortality) than in those who do (72% mortality). Predictors of mortality include mainly decreased urine volume (eg, anuria, oliguria) and severity of the underlying illness and comorbid disorders.

Cause of death is usually infection or the underlying disorder.

Treatment

• Supportive care

Treatment is supportive and includes stopping nephrotoxins whenever possible, maintenance of euvolemia, nutritional support, and treatment of infections (preferably with drugs that are not nephrotoxic). Diuretics are commonly used to maintain urine output in oliguric ATN but are of unproven benefit; there is no evidence to support use of mannitol or dopamine. General management of acute renal failure is discussed on p. 2440.

Prevention

Prevention includes the following:

• Maintaining euvolemia and renal perfusion in critically ill patients

• Avoiding nephrotoxic drugs when possible

• Closely monitoring renal function when nephrotoxic drugs must be used

• Taking measures to prevent contrast nephropathy

• Among patients with diabetes, controlling blood sugar levels

There is no evidence that loop diuretics, mannitol, or dopamine helps prevent ATN.

[**Table 236-1.** Laboratory Findings Distinguishing Acute Tubular Necrosis From Prerenal Azotemia]

Contrast Nephropathy

Contrast nephropathy is worsening of renal function after IV administration of radiocontrast and is usually temporary. Diagnosis is based on a progressive rise in serum creatinine 24 to 48 h after contrast is given. Treatment is supportive. Volume loading with isotonic saline before and after contrast administration may help in prevention.

All iodinated radiocontrast agents are nephrotoxic. However, risk is lower with newer contrast agents, which have a lower osmolality than older agents, whose osmolality is about 1400 to 1800 mOsm/kg. For example, 2nd-generation, low-osmolal agents (eg, iohexol, iopamidol, ioxaglate) have an osmolality of about 500 to 850 mOsm/kg, which is still higher than blood osmolality. Iodixanol, the first of the even newer iso-osmolal agents, has an osmolality of 290 mOsm/kg, about equal to that of blood.

The precise mechanism of radiocontrast toxicity is unknown but is suspected to be some combination of renal vasoconstriction and direct cytotoxic effects, perhaps through formation of reactive O_2 species, causing ATN.

Risk factors: Risk factors for nephrotoxicity are the following:

• Older age

• Preexisting renal insufficiency (eg, serum creatinine > 1.5 mg/dL)

• Diabetes mellitus

- Heart failure
- Multiple myeloma
- High doses (eg, > 100 mL) of a hyperosmolar contrast agent (eg, during percutaneous coronary interventions)
- Factors that reduce renal perfusion, such as volume depletion or the concurrent use of NSAIDs or ACE inhibitors

Diagnosis

Diagnosis is based on a progressive rise in serum creatinine 24 to 48 h after a contrast study. Most patients have no symptoms. Renal function typically later returns to normal.

After femoral artery catheterization, contrast nephropathy may be difficult to distinguish from renal atheroembolism. Factors that can suggest renal atheroemboli include the following:

- Delay in onset of increased creatinine > 48 h after the procedure
- Presence of other atheroembolic findings (eg, in skin, toes)
- Persistently poor renal function
- Transient eosinophilia or eosinophiluria and low complement levels (measured if atheroemboli are seriously considered)

Treatment

Treatment is supportive.

Prevention

Prevention involves avoiding contrast when possible (eg, not using CT to diagnose appendicitis) and, when contrast is necessary, using the agent with the lowest osmolality for patients with risk factors. When contrast is given, mild volume expansion with isotonic NaCl (ie, 154 mEq/L) is recommended; 1 mL/kg/h is given beginning 6 to 12 h before contrast is given and continued for 6 to 12 h after the procedure. Infusion of $NaHCO_3$ has no proven advantage over normal saline and may even be harmful. Nephrotoxic drugs are avoided before and after the procedure. Acetylcysteine is an antioxidant that may be helpful; protocols vary, but acetylcysteine, 600 mg po bid the day before and the day of the procedure, may be given, combined with NaCl infusion. Acetylcysteine and volume expansion may be most helpful in patients with mild preexisting renal disease and exposure to a low dose of contrast.

Periprocedural continuous venovenous hemofiltration has no proven benefit compared with other less invasive strategies in preventing acute kidney injury in patients who have chronic kidney disease and who require high doses of contrast and also is not practical. Therefore, this procedure is not recommended. Patients undergoing regular hemodialysis for end-stage renal disease who require contrast do not need supplementary, prophylactic hemodialysis after the procedure.

Tubulointerstitial Nephritis

Tubulointerstitial nephritis is primary injury to renal tubules and interstitium resulting in decreased renal function. The acute form is most often due to allergic drug reactions or to infections. The chronic form occurs with a diverse array of causes, including genetic or metabolic disorders, obstructive uropathy, and chronic exposure to environmental toxins or to certain drugs and herbs. Diagnosis is suggested by history and urinalysis and often confirmed by biopsy. Treatment and prognosis vary by the etiology and potential reversibility of the

disorder at the time of diagnosis.

Etiology

Tubulointerstitial nephritis can be primary, but a similar process can result from glomerular damage (see p. 2387) or renovascular disorders (see p. 2429).

Primary tubulointerstitial nephritis may be

• Acute (see Table 236-2)

• Chronic (see Table 236-3)

Acute tubulointerstitial nephritis (ATIN): ATIN involves an inflammatory infiltrate and edema affecting the renal interstitium that often develops over days to months. Over 95% of cases result from infection or an allergic drug reaction. A syndrome of ATIN associated with uveitis (renal-ocular syndrome) also occurs and is idiopathic. ATIN causes acute renal insufficiency or failure; severe cases, delayed therapy, or continuance of an offending drug can lead to permanent injury with chronic renal failure.

[**Table 236-2.** Causes of Acute Tubulointerstitial Nephritis]

[**Table 236-3.** Causes of Chronic Tubulointerstitial Nephritis]

Chronic tubulointerstitial nephritis (CTIN): CTIN arises when chronic tubular insults cause gradual interstitial infiltration and fibrosis, tubular atrophy and dysfunction, and a gradual deterioration of renal function, usually over years. Glomerular involvement (glomerulosclerosis) is much more common in CTIN than in ATIN. Causes of CTIN are myriad; they include immunologically mediated disorders, infections, reflux or obstructive nephropathy, drugs, and other disorders. CTIN due to toxins, metabolic derangements, hypertension, and inherited disorders results in symmetric and bilateral disease; with other causes, renal scarring may be unequal and involve only one kidney. Some well-characterized forms of CTIN include analgesic, metabolic, heavy metal, and reflux nephropathy and myeloma kidney (hereditary cystic kidney diseases are discussed in Ch. 234).

Symptoms and Signs

ATIN: Symptoms and signs of ATIN may be nonspecific and are often absent unless symptoms and signs of renal failure develop. Many patients develop polyuria and nocturia (due to a defect in urinary concentration and Na reabsorption). Symptom onset may be as long as several weeks after initial toxic exposure or as soon as 3 to 5 days after a 2nd exposure; extremes in latency range from 1 day with rifampin to 18 mo with an NSAID. Fever and urticarial rash are characteristic early manifestations of drug-induced ATIN, but the classically described triad of fever, rash, and eosinophilia is insensitive. Abdominal pain, weight loss, and bilateral renal masses (caused by interstitial edema) may also occur in ATIN and with fever may mistakenly suggest renal cancer or polycystic kidney disease. Peripheral edema and hypertension are uncommon unless renal insufficiency or renal failure occurs.

CTIN: Symptoms and signs are generally absent in CTIN unless renal failure develops. Edema usually is not present, and BP is normal or only mildly elevated in the early stages. Polyuria and nocturia may develop.

Diagnosis

• Risk factors

• Active urinary sediment, particularly with sterile pyuria (including eosinophils)

• Sometimes biopsy

Few clinical and routine laboratory findings are specific. Thus, suspicion should be high when the following are present:

- Typical symptoms or signs
- Risk factors, particularly a temporal relationship between onset and use of a potentially causative drug
- Characteristic urinalysis findings, particularly sterile pyuria (including eosinophils)
- Modest proteinuria, usually < 1 g/day (except with use of NSAIDs, which may cause nephrotic-range proteinuria)
- Evidence of tubular dysfunction (eg, renal tubular acidosis, Fanconi syndrome)

Other tests (eg, imaging) may be necessary to differentiate ATIN or CTIN from other disorders. Renal biopsy is sometimes done.

ATIN: Signs of active kidney inflammation (active urinary sediment), including RBCs, WBCs, and WBC casts, and absence of bacteria on culture (sterile pyuria) are typical; marked hematuria and dysmorphic RBCs are uncommon. Eosinophiluria has a positive predictive value of 50% (specificity of about 85 to 93%) and a negative predictive value of up to 90% for ATIN (sensitivity of about 63 to 91%). Thus, the presence of urinary eosinophils is not diagnostic, but their absence significantly decreases the likelihood of the diagnosis. Proteinuria is usually minimal but may reach nephrotic range with combined ATIN-glomerular disease induced by NSAIDs, ampicillin, rifampin, interferon alfa, or ranitidine. Blood test findings of tubular dysfunction include hypokalemia (caused by a defect in K reabsorption) and a nonanion gap metabolic acidosis (caused by a defect in HCO_3 reabsorption or acid excretion).

Ultrasonography, radionuclide scanning, or both may be needed to differentiate ATIN from other causes of acute renal failure, such as acute tubular necrosis. In ATIN, ultrasonography may show kidneys that are greatly enlarged and echogenic because of interstitial inflammatory cells and edema. Radionuclide scans may show kidneys avidly taking up radioactive gallium-67 or radionuclide-labeled WBCs. Positive scans strongly suggest ATIN (and indicate that acute tubular necrosis is less likely), but a negative scan does not exclude ATIN.

Renal biopsy is usually reserved for patients with the following:

- An uncertain diagnosis
- Progressive renal injury
- No improvement after potential causative drugs are stopped

In ATIN, glomeruli are usually normal. The earliest finding is interstitial edema, typically followed by interstitial infiltration with lymphocytes, plasma cells, eosinophils, and a few PMNs. In severe cases, inflammatory cells can be seen invading the space between the cells lining the tubular basement membrane (tubulitis); in other specimens, granulomatous reactions resulting from exposure to methicillin, sulfonamides, mycobacteria, or fungi may be seen. The presence of noncaseating granulomas suggests sarcoidosis. Immunofluorescence or electron microscopy seldom reveals any pathognomonic changes.

CTIN: Findings of CTIN are generally similar to those of ATIN, although urinary RBCs and WBCs are uncommon. Because CTIN is insidious in onset and interstitial fibrosis is common, imaging tests may show small kidneys with evidence of scarring and asymmetry.

In CTIN, renal biopsy is not often done for diagnostic purposes but has helped characterize the nature and progression of tubulointerstitial disease. Glomeruli vary from normal to completely destroyed. Tubules may be absent or atrophied. Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts. The interstitium contains varying degrees of inflammatory cells and fibrosis.

Nonscarred areas appear almost normal. Grossly, the kidneys are small and atrophic.

Prognosis

In drug-induced ATIN, renal function usually recovers within 6 to 8 wk when the offending drug is stopped, although some residual scarring is common. Recovery may be incomplete, with persistent azotemia above baseline. When other factors cause ATIN, histologic changes usually are reversible if the cause is recognized and removed; however, some severe cases progress to fibrosis and renal failure. Regardless of cause, irreversible injury is suggested by the following:

• Diffuse rather than patchy interstitial infiltrate

• Significant interstitial fibrosis

• Delayed response to prednisone

• Acute kidney injury lasting > 3 wk

In CTIN, prognosis depends on the cause and on the ability to recognize and stop the process before irreversible fibrosis occurs. Many genetic (eg, cystic kidney disease), metabolic (eg, cystinosis), and toxic (eg, heavy metal) causes may not be modifiable, in which case CTIN usually evolves to end-stage renal disease.

Treatment

• Treatment of cause

• Corticosteroids for immune-mediated and sometimes drug-induced tubulointerstitial nephritis

Treatment of both ATIN and CTIN is management of the cause. For immunologically induced disease in ATIN and perhaps CTIN and sometimes drug-induced ATIN, corticosteroids (eg, prednisone 1 mg/kg po once/day with gradual tapering of the dose over 4 to 6 wk) may accelerate recovery. Treatment of CTIN often requires supportive measures such as controlling BP and treating anemia associated with kidney disease. In patients with CTIN and progressive renal injury, ACE inhibitors or angiotensin II receptor blockers may slow disease progression.

Analgesic Nephropathy

Analgesic nephropathy (AN) is CTIN caused by cumulative lifetime use of large amounts (eg, ≥ 2 kg) of certain analgesics.

AN was originally described in conjunction with overuse of combination analgesics containing phenacetin (typically with aspirin, acetaminophen, codeine, or caffeine). However, despite removal of phenacetin from the market, AN continued to occur. Studies to identify the causal agent are equivocal, but acetaminophen, aspirin, and other NSAIDs have been implicated. Mechanism is unclear. Whether COX-2 inhibitors cause AN is not known, but these drugs probably can cause ATIN and nephrotic syndrome due to minimal change disease or membranous nephropathy.

AN predominates in women (peak incidence, 50 to 55 yr) and, in the US, is responsible for 3 to 5% of cases of end-stage renal disease (13 to 20% in Australia and South Africa).

Patients present with renal insufficiency and usually non-nephrotic proteinuria with a bland urinary sediment or sterile pyuria. Hypertension, anemia, and impaired urinary concentration are common once renal insufficiency develops. Flank pain and hematuria are signs of papillary necrosis that occur late in the course of disease. Chronic complaints of musculoskeletal pain, headache, malaise, and dyspepsia may be related to long-term analgesic use rather than AN.

Diagnosis is based on history of chronic analgesic use and noncontrast CT. CT signs of AN are the

following:

• Decreased renal size

• Bumpy contours, defined as at least 3 indentations in the normally convex outline of the kidney

• Papillary calcifications

The combination of these findings has a sensitivity of 85% and a specificity of 93% for early diagnosis, but these specificity and sensitivity numbers are based on studies done when use of phenacetin-containing analgesics was widespread.

Renal function stabilizes when analgesics are stopped unless renal insufficiency is advanced, in which case it may progress to renal failure. Patients with AN are at greater risk of transitional cell carcinomas of the urinary tract.

Metabolic Nephropathies

Tubulointerstitial disorders can result from several metabolic disturbances.

Acute urate nephropathy: This disorder is not a true form of ATIN but rather an intraluminal obstructive uropathy caused by uric acid crystal deposition within the lumen of renal tubules; acute oliguric or anuric kidney injury results. Causes include the following:

• Tumor lysis syndrome (see p. 1075) after treatment of lymphoma, leukemia, or other myeloproliferative disorders (the most common cause)

• Seizures

• Treatment of solid tumors

• Rare primary disorders of urate overproduction (hypoxanthine-guanine phosphoribo-syltransferase deficiency) or overexcretion due to decreased proximal tubule reabsorption (Fanconi-like syndromes).

Typically, no symptoms are present. Diagnosis is suspected when acute kidney injury occurs in patients with marked hyperuricemia (> 15 mg/dL). Urinalysis results may be normal or may show urate crystals.

Prognosis for complete recovery of renal function is excellent if treatment is initiated rapidly. Treatment is usually with allopurinol plus aggressive IV hydration in patients with normal cardiac and renal function. Supportive measures are indicated. Hemodialysis may be recommended to remove excess circulating urate in severe cases where diuresis cannot be induced with a loop diuretic and IV saline.

Prevention is indicated for patients at high risk (eg, those at risk of tumor lysis syndrome). Prevention is by use of allopurinol 300 mg po bid to tid plus saline loading to maintain a urine output > 2.5 L/day before chemotherapy or radiation therapy. Urate oxidase (rasburicase), which catalyzes urate to a much more soluble compound, is also preventive and is being more commonly used in patients with severe hyperuricemia. However, patients given rasburicase must be carefully monitored because the drug must be given IV and can cause anaphylaxis, hemolysis, and other adverse effects.

Chronic urate nephropathy: This condition is CTIN caused by deposition of Na urate crystals in the medullary interstitium in patients with chronic hyperuricemia. Sequelae are chronic inflammation and fibrosis, with ensuing chronic renal insufficiency and renal failure. Chronic urate nephropathy was once common in patients with tophaceous gout but is now rare because gout is more often effectively treated. A bland urine sediment and hyperuricemia disproportionate to the degree of renal insufficiency (eg, urate > 9 mg/dL with serum creatinine < 1.5 mg/dL, or > 10 mg/dL with serum creatinine 1.5 to 2 mg/dL, and > 12 mg/dL with more advanced renal failure) are suggestive but nonspecific; many causes of tubulointerstitial diseases may have these findings, lead nephropathy being the most common. Treatment is that of hyperuricosuria (see p. 353).

Hyperoxaluria: Hyperoxaluria is a common cause of nephrolithiasis but an uncommon cause of acute and chronic tubulointerstitial nephritis. Causes and prevention of hyperoxaluria are discussed elsewhere (see p. 2369).

Hypercalcemia: Hypercalcemia (see p. 843) causes nephropathy by 2 mechanisms. Severe (> 12 mg/dL) temporary hypercalcemia may cause reversible renal insufficiency by renal vasoconstriction and natriuresis-induced volume depletion. Long-standing hypercalcemia and hypercalciuria lead to CTIN with calcification and necrosis of tubular cells, interstitial fibrosis, and calcification (nephrocalcinosis). Common associated findings include

• Nephrolithiasis

• Renal tubular acidosis

• Nephrogenic diabetes insipidus

Diagnosis is based on presence of hypercalcemia and unexplained renal insufficiency; nephrocalcinosis can be detected by ultrasonography or noncontrast CT. Treatment is management of hypercalcemia.

Chronic hypokalemia: Chronic hypokalemia of a moderate to severe degree may cause nephropathy with impaired urinary concentration and vacuolation of proximal tubular cells and occasionally of distal tubular cells. Chronic interstitial inflammatory changes, fibrosis, and renal cysts have been found in renal biopsies of patients with hypokalemia of ≥ 1 mo. Treatment consists of correction of the underlying disorder and oral K supplements. Although the hypokalemia as well as the number and size of the cysts are reversible, the CTIN and renal insufficiency may be irreversible.

Heavy Metal Nephropathy

Exposure to heavy metals and other toxins can result in tubulointerstitial disorders.

Lead: CTIN results as lead accumulates in proximal tubular cells. Short-term lead exposure causes proximal tubular dysfunction, including decreased urate secretion and hyperuricemia (urate is the substrate for saturnine gout), aminoaciduria, and renal glucosuria. Chronic lead exposure (ie, for 5 to ≥ 30 yr) causes progressive tubular atrophy and interstitial fibrosis, with renal insufficiency, hypertension, and gout. However, chronic low-level exposure may cause renal insufficiency and hypertension independent of tubulointerstitial disease. The following groups are at highest risk:

• Children exposed to lead paint dust or chips

• Welders

• Battery workers

• Drinkers of moonshine alcohol

Exposed children may develop nephropathy during adulthood.

Hyperuricemia disproportionate to the degree of renal insufficiency (eg, urate > 9 mg/dL with serum creatinine < 1.5 mg/dL, or > 10 mg/dL with serum creatinine 1.5 to 2 mg/dL, and > 12 mg/dL with more advanced renal failure) and a bland urinary sediment are common. Diagnosis is usually made by measuring whole blood lead levels. Alternatively, x-ray fluorescence may be used to detect increased bone lead concentrations, which reflect high cumulative lead exposure. Treatment with chelation therapy (see p. 3344) can stabilize renal function, but recovery may be incomplete.

Cadmium: Cadmium from contaminated water, food, and tobacco and, mainly, from workplace exposures can cause nephropathy. It can also cause a glomerulopathy that is usually asymptomatic. Early manifestations of cadmium nephropathy are those of tubular dysfunction, including low molecular weight

tubular proteinuria (eg, β_2-microglobulin), aminoaciduria, and renal glucosuria. Symptoms and signs, when they occur, are attributable to chronic renal insufficiency and failure. Renal disease follows a dose-response curve. Diagnosis is likely with the following:

- History of occupational exposure
- Increased levels of urinary β_2-microglobulin (missed by urinary dipstick protein testing but detected using radioimmunoassay)
- Increased urinary cadmium levels (> 7 µg/g creatinine)

Treatment is elimination of cadmium exposure; chelation with Na calcium edetate (EDTA) may increase cadmium nephrotoxicity. Tubular proteinuria usually is irreversible.

Other heavy metals: Other heavy metals that are nephrotoxic include

- Copper
- Gold
- Uranium
- Arsenic
- Iron
- Mercury
- Bismuth
- Chromium

All cause tubular damage and dysfunction (eg, tubular proteinuria, aminoaciduria) as well as tubular necrosis, but glomerulopathies may predominate with some compounds (mercury, gold). Treatment involves removal of the patient from further exposure and either or both of the following:

- Chelating agents (copper, arsenic, bismuth)
- Dialysis (chromium, arsenic, bismuth), often used when chelation fails or simultaneously with chelation for severe arsenic poisoning

Reflux Nephropathy

Reflux nephropathy is renal scarring presumably induced by vesicoureteral reflux of infected urine into the renal parenchyma. The diagnosis is suspected in children with UTI or a family history. Diagnosis is by voiding cystourethrography or radionuclide cystography. Children with moderate or severe reflux are treated with prophylactic antibiotics or surgical correction.

Traditionally, the mechanism of renal scarring has been thought to be chronic pyelonephritis. However, reflux is probably the single most important factor, and factors unrelated to reflux or pyelonephritis (eg, congenital factors) can contribute. Vesicoureteral reflux (VUR) affects about 1% of newborns and 30 to 45% of young children with a febrile UTI (see p. 2844); it is common among children with renal scars and, for unknown reasons, is less common among black children than white children. Familial predisposition is common. Children with gross reflux (up to the renal pelvis plus ureteral dilatation) are at highest risk of scarring and subsequent renal failure.

Reflux requires incompetent ureterovesical valves or mechanical obstruction in the lower urinary tract. Young children with shorter intravesical portions of the ureter are most susceptible; normal growth usually

results in spontaneous cessation of intrarenal and vesicoureteral reflux by age 5. New scars in children > 5 yr are unusual but may occur after acute pyelonephritis.

Symptoms and Signs

Few symptoms and signs other than occasional UTI are present in young children, and the diagnosis is often overlooked until adolescence, when patients present with polyuria, nocturia, hypertension, symptoms and signs of renal insufficiency, laboratory abnormalities, or a combination.

Diagnosis

• Voiding cystourethrography or radionuclide cystography

The diagnosis may be suspected prenatally or postnatally. Diagnosis and staging of reflux nephropathy (prenatal or postnatal presentation) are made by a voiding cystourethrogram (VCUG), which can demonstrate the degree of ureteral dilatation. Radionuclide cystography (RNC) can also be used; it provides less anatomic detail than VCUG but involves less radiation exposure. Because these tests involve catheterization (and risk of UTI) as well as radiation exposure, thresholds for obtaining them can be controversial. Renal scarring is diagnosed with technetium-99m-labeled dimercaptosuccinic acid (DMSA) radionuclide scanning.

Prenatal presentation: The diagnosis is suspected prenatally if ultrasonography, done because of a family history or for unrelated reasons, shows hydronephrosis; 10 to 40% of such patients are diagnosed postnatally with VUR. Some experts recommend VCUG or RNC only if family history is strong or if postnatal renal ultrasonography is markedly or persistently abnormal; however, it is not clear whether renal ultrasonography is sufficiently sensitive to detect VUR. DMSA scanning is typically done in neonates (as well as infants < 6 mo) who have worrisome UTIs (eg, febrile or recurrent UTIs).

Postnatal presentation: VUR is suspected postnatally in patients with any of the following:

• UTI at age ≤ 3 yr

• Febrile UTI at age ≤ 5 yr

• Recurrent UTIs in children

• UTI in males

• Strong family history, such as a sibling with VUR (controversial)

• Adults (or children > 5 yr) with recurrent UTI in whom renal ultrasonography reveals scarring or a urinary tract anatomic abnormality

Laboratory abnormalities may include proteinuria, Na wasting, hyperkalemia, metabolic acidosis, renal insufficiency, or a combination. Testing for these patients is with RNC or VCUG. DMSA scanning may be done for infants or children with UTIs as listed above.

In older children in whom reflux is no longer active, a VCUG may not show reflux, although the DMSA scan shows scarring; cystoscopy can demonstrate evidence of previous reflux at ureteral orifices. Thus, DMSA scanning and cystoscopy may be done if prior reflux is suspected but not confirmed. Renal biopsy at this late stage shows CTIN and focal glomerulosclerosis, the cause of mild (1 to 1.5 g/day) to nephrotic-range proteinuria.

Treatment

• Usually prophylactic antibiotics

• Surgical treatment if VUR is moderate or severe

Treatment is based on the unproven assumption that decreasing reflux and UTIs prevents renal scarring. Children with very mild VUR require no treatment, but they should be closely observed for symptoms of UTI. Children with moderate reflux are usually given antibiotics. However, drug therapy predisposes to new episodes of acute pyelonephritis, and it is not clear whether prophylactic antibiotics are more effective than close observation. Patients with severe reflux are at higher risk of renal insufficiency and are usually given antibiotic prophylaxis or undergo surgical interventions, including ureteral reimplantation or endoscopic injection of materials behind the ureter to prevent reflux (bladder contraction during voiding compresses the ureter between the bladder and the material). Incidence of new renal scars is similar in patients treated with surgery and with drugs.

Reflux spontaneously resolves in about 80% of young children within 5 yr.

Myeloma-Related Kidney Disease

Patients with multiple myeloma overproduce monoclonal Ig light chains (Bence Jones proteins); these light chains are filtered by glomeruli, are nephrotoxic, and can damage virtually all areas of the kidney parenchyma. Diagnosis is by urine tests (sulfosalicylic acid test or protein electrophoresis) or renal biopsy. Treatment focuses on the multiple myeloma and ensuring adequate urine flow.

Tubulointerstitial and glomerular damage are the most common types of renal damage. The mechanisms by which light chains damage nephrons directly are unknown. Hypercalcemia contributes to renal insufficiency by decreasing renal blood flow.

Tubulointerstitial disease: Light chains saturate the reabsorptive capacity of the proximal tubule, reach the distal nephron, and combine with filtered proteins and Tamm-Horsfall mucoprotein (secreted by cells of the thick ascending limb of Henle) to form obstructive casts. The term myeloma kidney or myeloma cast nephropathy generally refers to renal insufficiency caused by the tubulointerstitial damage that results. Factors that predispose to cast formation include the following:

• Low urine flow

• Radiocontrast agents

• Hyperuricemia

• NSAIDs

• Elevation of luminal NaCl concentration (eg, due to a loop diuretic)

• Increased intratubular Ca from the hypercalcemia that often occurs secondary to bone lysis in multiple myeloma

Other types of tubulointerstitial lesions that occur with Bence Jones proteinuria include proximal tubular transport dysfunction causing Fanconi syndrome and light chain interstitial deposition with inflammatory infiltrates and active tubular damage.

Glomerulopathies: Myeloma glomerulopathy has 2 common mechanisms: primary (AL) amyloidosis (see also p. 905) and glomerular light chain or rarely heavy chain deposition. AL amyloidosis results in glomerular deposition of AL amyloid in the mesangial, subepithelial, or subendothelial areas or a combination. Amyloid deposition is with randomly oriented, nonbranching fibrils composed of the variable regions of λ light chains. Light chain deposition disease (LCDD), which also can occur with lymphoma and Waldenstrom's macroglobulinemia, is glomerular deposition of nonpolymerized light chains (ie, without fibrils), generally the constant regions of κ chains.

Rarely, a nonproliferative, noninflammatory glomerulopathy that causes nephrotic-range proteinuria can develop in advanced myeloma-related renal disease. A proliferative glomerulonephritis occasionally

develops as an early form of LCDD with progression to membranoproliferative glomerulonephritis and nodular glomerulopathy reminiscent of diabetic nephropathy; nephrotic-range proteinuria is common.

Symptoms and Signs

Symptoms and signs are predominantly those of the myeloma (eg, skeletal pain, pathologic fractures, diffuse osteoporosis) and a normochromic-normocytic anemia.

Diagnosis

• Urine sulfosalicylic acid test or urine protein electrophoresis (myeloma kidney)

• Biopsy (glomerulopathy)

Diagnosis of myeloma-related kidney disease is suggested by the following combination of findings:

• Renal insufficiency

• Bland urine sediment

• Negative or trace-positive dipstick for protein (unless urine albumin is elevated in a patient with an accompanying nephrotic syndrome)

The diagnosis should be suspected even in patients without a history of or findings suggesting multiple myeloma. Diagnosis of light chain tubulointerstitial disease (myeloma kidney) is confirmed by a markedly positive urine sulfosalicylic acid test suggesting significant nonalbumin proteins, by urine protein electrophoresis (UPEP), or both. Diagnosis of glomerulopathy is confirmed by renal biopsy. Renal biopsy may demonstrate light chain deposition in 30 to 50% of patients with myeloma despite the absence of detectable serum or urine paraproteins by immuno-electrophoresis.

Prognosis

Kidney disease is a major predictor of overall prognosis in multiple myeloma. Prognosis is good for patients with tubulointerstitial and glomerular LCDD who receive treatment. Prognosis is worse for patients with AL amyloidosis, in whom amyloid deposition continues and progresses to renal failure in most cases. In either form without treatment, virtually all renal lesions progress to renal failure.

Treatment

• Management of multiple myeloma

• Prevention of volume depletion and maintenance of a high urine flow rate

Management of multiple myeloma (see p. 1031), prevention of volume depletion, and maintenance of a high urine flow rate are the primary treatments. In addition, factors that worsen renal function (eg, hypercalcemia, hyperuricemia, use of nephrotoxic drugs) should be avoided or treated. Several measures are often recommended but are of unproven efficacy. Plasmapheresis may be tried to remove light chains. Alkalinization of the urine to help change the net charge of the light chain and reduce charge interaction with Tamm-Horsfall mucoprotein may make the light chains more soluble. Colchicine may be given to decrease secretion of Tamm-Horsfall mucoprotein into the lumen and to decrease the interaction with light chains, thus decreasing toxicity. Loop diuretics may be avoided to prevent volume depletion and high distal Na concentrations that can worsen myeloma-related kidney disease (loop diuretics are indicated if hypercalcemia is present).

Chapter 237. Renal Transport Abnormalities

Introduction

Many substances are secreted or reabsorbed in the renal tubule system, including electrolytes, protons, HCO_3 molecules, and free water. Dysfunction of these processes can result in clinical syndromes. Syndromes are inherited, acquired, or both. Syndromes that almost always manifest in childhood (eg, Bartter syndrome, Gitelman's syndrome, cystinuria, Hartnup disease, and hypophosphatemic rickets) are discussed in Ch. 297.

Fanconi Syndrome

Fanconi syndrome consists of multiple defects in renal proximal tubular reabsorption, causing glucosuria, phosphaturia, generalized aminoaciduria, and HCO_3 wasting. Symptoms in children are failure to thrive, growth retardation, and rickets. Symptoms in adults are osteomalacia and muscle weakness. Diagnosis is by showing glucosuria, phosphaturia, and aminoaciduria. Treatment is HCO_3 replacement and measures directed at renal failure.

Etiology

Fanconi syndrome can be

• Hereditary

• Acquired

Hereditary Fanconi syndrome: This disorder usually accompanies another genetic disorder, particularly cystinosis. Cystinosis is an inherited (autosomal recessive) metabolic disorder in which cystine accumulates within cells and tissues (and is not excreted to excess in the urine as occurs in cystinuria—see p. 2990). Besides renal tubular dysfunction, other complications of cystinosis include eye disorders, hepatomegaly, hypothyroidism, and other manifestations.

Fanconi syndrome may also accompany Wilson's disease, hereditary fructose intolerance, galactosemia, glycogen storage disease, oculocerebrorenal syndrome (Lowe syndrome), mitochondrial cytopathies, and tyrosinemia. Inheritance patterns vary with the associated disorder.

Acquired Fanconi syndrome: This disorder may be caused by various drugs, including certain cancer chemotherapy drugs (eg, ifosfamide, streptozocin), antiretrovirals (eg, didanosine, cidofovir), and outdated tetracycline. All of these drugs are nephrotoxic. Acquired Fanconi syndrome also may occur after renal transplantation and in patients with multiple myeloma, amyloidosis, intoxication with heavy metals or other chemicals, or vitamin D deficiency.

Pathophysiology

Various defects of proximal tubular transport function occur, including impaired resorption of glucose, phosphate, amino acids, HCO_3, uric acid, water, K, and Na. The aminoaciduria is generalized, and, unlike that in cystinuria, increased cystine excretion is a minor component. The basic pathophysiologic abnormality is unknown but may involve a mitochondrial disturbance. Low levels of serum phosphate cause rickets, which is worsened by decreased proximal tubular conversion of vitamin D to its active form.

Symptoms and Signs

In hereditary Fanconi syndrome, the chief clinical features—proximal tubular acidosis, hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia—usually appear in infancy.

When Fanconi syndrome occurs because of cystinosis, failure to thrive and growth retardation are common. The retinas show patchy depigmentation. Interstitial nephritis develops, leading to progressive

renal failure that may be fatal before adolescence.

In acquired Fanconi syndrome, adults present with the laboratory abnormalities of renal tubular acidosis (proximal type 2), hypophosphatemia, and hypokalemia. They may present with symptoms of bone disease (osteomalacia) and muscle weakness.

Diagnosis

• Urine testing for glucose, phosphates, and amino acids

Diagnosis is made by showing the abnormalities of renal function, particularly glucosuria (in the presence of normal serum glucose), phosphaturia, and aminoaciduria. In cystinosis, slit-lamp examination may show cystine crystals in the cornea.

Treatment

• Sometimes $NaHCO_3$ or $KHCO_3$ or Na citrate or K citrate

• Sometimes K supplementation

Other than removing the offending nephrotoxin, there is no specific treatment. Acidosis may be lessened by giving tablets or solutions of Na or K HCO_3 or citrate, eg, Shohl's solution (Na citrate and citric acid; 1 mL is equivalent to 1 mmol of HCO_3) given 1 mEq/kg bid to tid or 5 to 15 mL after meals and at bedtime. K depletion may require replacement therapy with a K-containing salt. Hypophosphatemic rickets can be treated (see p. 2991). Renal transplantation has been successful in treating renal failure. However, when cystinosis is the underlying disease, progressive damage may continue in other organs and eventually result in death.

Liddle Syndrome

Liddle syndrome is a rare hereditary disorder in which the kidneys excrete K but retain too much Na and water, leading to hypertension. Symptoms are of hypertension, fluid retention, and metabolic alkalosis. Diagnosis is through measurement of urinary electrolytes. K-sparing diuretics provide the best treatment.

Liddle syndrome is a rare autosomal dominant disorder of renal epithelial transport that clinically resembles primary aldosteronism (see p. 799), with hypertension and hypokalemic metabolic alkalosis but without elevated plasma renin or aldosterone levels. The syndrome results from an inherently increased activity of the luminal membrane Na channels, which accelerates Na resorption and K secretion in the collecting tubule.

Patients with Liddle syndrome present at age < 35 yr. Hypertension and symptoms and signs of hypokalemia (see p. 832) and metabolic alkalosis occur.

Diagnosis

• Urine Na level

• Plasma renin and aldosterone levels

Diagnosis is suggested by the presence of hypertension in a young patient, particularly one with a positive family history. Low urine Na (< 20 mEq), normal plasma renin and aldosterone levels, and response to empiric treatment usually are considered sufficient to confirm the diagnosis. Definitive diagnosis can be achieved through genetic testing.

Treatment

Triamterene 100 to 200 mg po bid and amiloride 5 to 20 mg po once/day are both effective because they close Na channels. Spironolactone is ineffective.

Nephrogenic Diabetes Insipidus

(See also Central Diabetes Insipidus on p. 772.)

Nephrogenic diabetes insipidus (NDI) is an inability to concentrate urine due to impaired renal tubule response to ADH (vasopressin), which leads to excretion of large amounts of dilute urine. It can be inherited or occur secondary to conditions that impair renal concentrating ability. Symptoms and signs include polyuria and those related to dehydration and hypernatremia. Diagnosis is based on measurement of urine osmolality changes after water deprivation and administration of exogenous ADH. Treatment consists of adequate free water intake, thiazide diuretics, NSAIDs, and a low-salt, low-protein diet.

NDI is characterized by inability to concentrate urine in response to ADH. Central diabetes insipidus is characterized by lack of ADH. Either type of diabetes insipidus may be complete or partial.

Etiology

NDI can be

• Inherited

• Acquired

Inherited NDI: The most common inherited disorder is an X-linked trait that affects the arginine vasopressin (AVP) receptor 2 gene. In rare cases, NDI is caused by an autosomal recessive or autosomal dominant mutation that affects the aquaporin-2 gene. Except with the autosomal dominant form, patients who are homozygous are completely unresponsive to ADH. Patients who are heterozygous have normal or slightly impaired responsiveness to ADH.

Acquired NDI: Acquired NDI can occur when disorders (some of them heritable) or drugs disrupt the medulla or distal nephrons and impair urine concentrating ability, making the kidneys appear insensitive to ADH. These disorders include the following:

• Autosomal dominant polycystic kidney disease

• Nephronophthisis and medullary cystic kidney disease

• Sickle cell nephropathy

• Release of obstructing periureteral fibrosis

• Medullary sponge kidney

• Pyelonephritis

• Hypokalemic and hypercalcemic nephropathies

• Amyloidosis

• Sjogren's syndrome

• Bardet-Biedl syndrome

• Certain cancers (eg, myeloma, sarcoma)

- Many drugs, especially lithium, but also others (eg, demeclocycline, amphotericin B, aminoglycosides, cidofovir, cisplatin, foscarnet, ifosfamide, methoxyflurane, ofloxacin, orlistat, rifampin)

Acquired NDI can also be idiopathic. A mild form of acquired NDI can occur in any patient who is elderly or sick or who has acute or chronic renal insufficiency.

In addition, certain clinical syndromes can resemble NDI:

- The placenta can secrete vasopressinase during the 2nd half of pregnancy (a syndrome called gestational diabetes insipidus).

- After pituitary surgery, some patients secrete an ineffective ADH precursor rather than ADH.

Symptoms and Signs

Generation of large amounts of dilute urine (3 to 20 L/day) is the hallmark. Patients typically have a good thirst response, and serum Na remains near normal. However, patients who do not have good access to water or who cannot communicate thirst (eg, infants, elderly patients with dementia) typically develop hypernatremia from extreme dehydration. Hypernatremia may cause neurologic symptoms, such as neuromuscular excitability, confusion, seizures, or coma.

Infants with inherited NDI may develop brain damage with permanent intellectual disability if treatment is not started early. Even with treatment, physical growth is often retarded in affected children presumably because of frequent dehydration.

Diagnosis

- 24-h urine volume and osmolality

- Serum electrolytes

- Water deprivation test

NDI is suspected in any patient with polyuria (see also p. 2324). Initial testing includes 24-h urine collection (without fluid restriction) for volume and osmolality, and serum electrolytes.

Patients with NDI excrete > 50 mL/kg of urine/day (polyuria). If urine osmolality is < 300 mOsm/kg (water diuresis), central or nephrogenic diabetes insipidus is likely. With NDI, urine osmolality is typically < 200 mOsm/kg despite clinical signs of hypovolemia (normally, urine osmolality is high in patients with hypovolemia). If osmolality is > 300 mOsm/kg, solute diuresis is likely. Glucosuria and other causes of solute diuresis must be excluded.

Serum Na is mildly elevated (142 to 145 mEq/L) in patients with adequate free water intake but can be dramatically elevated in patients who do not have adequate access to free water.

The diagnosis is confirmed by a water deprivation test (see p. 773), which assesses the maximum urine concentrating ability and response to exogenous ADH. After 3 to 6 h of water deprivation, the maximal osmolality of urine in patients with NDI is abnormally low (< 400 mOsm/kg, usually < 300 mOsm/kg). NDI can be distinguished from central diabetes insipidus (lack of ADH) by administering exogenous ADH (aqueous vasopressin 5 units sc or desmopressin 10 µg intranasally) and measuring urine osmolality. In patients with central diabetes insipidus (see p. 772), urine osmolality increases 50 to 100% over the 2 h after administration of exogenous ADH (15 to 45% in partial central diabetes insipidus). Patients with NDI usually have only a minimal rise in urine osmolality (< 50 mOsm/kg; up to 45% in partial NDI).

Treatment

- Adequate free water intake

• Restriction of dietary salt and protein

• Correction of the cause

• Sometimes a thiazide diuretic, an NSAID, or amiloride

Treatment consists of ensuring adequate free water intake; providing a low-salt, low-protein diet; and correcting the cause or stopping any likely nephrotoxin. Serious sequelae are rare if patients can drink at will.

If symptoms persist despite these measures, drugs can be given to lower urine output. Thiazide diuretics (hydrochlorothiazide, 25 mg po once/day or bid) can paradoxically reduce urine output by diminishing water delivery to ADH-sensitive sites in the collecting tubules. NSAIDs (eg, indomethacin) or amiloride can also help.

Renal Glucosuria

(Renal Glycosuria)

Renal glucosuria is glucose in the urine without hyperglycemia; it results from either an acquired or an inherited, isolated defect in glucose transport or occurs with other renal tubule disorders.

Renal glucosuria is the excretion of glucose in the urine in the presence of normal blood glucose levels. The inherited form usually involves a reduction in the glucose transport maximum (the maximum rate at which glucose can be resorbed) and subsequent escape of glucose in the urine. The acquired form of renal glucosuria occurs primarily in advanced chronic kidney disease.

The inherited disorder is usually transmitted as an autosomal dominant trait but is occasionally recessive. Renal glucosuria may occur without any other abnormalities of renal function or as part of a generalized defect in proximal tubule function (see p. 2427). It also may occur with various systemic disorders, including Fanconi syndrome, cystinosis, Wilson's disease, hereditary tyrosinemia, and oculocerebrorenal syndrome (Lowe syndrome).

Renal glucosuria is asymptomatic and without serious sequelae. However, if there is an associated generalized defect in proximal tubular function, symptoms and signs may include hypophosphatemic rickets, volume depletion, short stature, muscle hypotonia, and ocular changes of cataracts or glaucoma (oculocerebrorenal syndrome) or Kayser-Fleischer rings (Wilson's disease). With such findings, transport defects other than glucosuria should be sought.

The disorder is typically initially noted on routine urinalysis. Diagnosis is based on finding glucose in a 24-h urine collection (when the diet contains 50% carbohydrate) in the absence of hyperglycemia (serum glucose < 140 mg/dL). To confirm that the excreted sugar is glucose and to exclude pentosuria, fructosuria, sucrosuria, maltosuria, galactosuria, and lactosuria, the glucose oxidase method should be used for all laboratory measurements. A normal result on an oral glucose tolerance test is also required for the diagnosis according to some experts.

Isolated renal glucosuria is benign; no treatment is necessary.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is acidosis and electrolyte disturbances due to impaired renal hydrogen ion excretion (type 1), impaired HCO_3 resorption (type 2), or abnormal aldosterone production or response (type 4). (Type 3 is extremely rare and is not discussed.) Patients may be asymptomatic, display symptoms and signs of electrolyte derangements, or progress to chronic kidney disease. Diagnosis is based on characteristic changes in urine pH and electrolytes in response to provocative testing. Treatment corrects pH and electrolyte imbalances using alkaline agents, electrolytes, and, rarely, drugs.

RTA defines a class of disorders in which excretion of hydrogen ions or reabsorption of filtered HCO_3 is impaired, leading to a chronic metabolic acidosis (see p. 859) with a normal anion gap. Hyperchloremia is usually present, and secondary derangements may involve other electrolytes, such as K (frequently) and Ca (rarely—see Table 237-1).

Chronic RTA is often associated with structural damage to renal tubules and may progress to chronic kidney disease (see p. 2442).

Type 1 (distal) RTA: Type 1 is impairment in hydrogen ion secretion in the distal tubule, resulting in a persistently high urine pH (> 5.5) and systemic acidosis. Plasma HCO_3 is usually < 15 mEq/L, and hypokalemia, hypercalciuria, and decreased citrate excretion are often present. Hypercalciuria is the primary abnormality in some familial cases, with Ca-induced tubulointerstitial damage causing distal RTA. Nephrocalcinosis and nephrolithiasis are possible complications of hypercalciuria and hypocitraturia if urine is relatively alkaline.

This syndrome is rare. Sporadic cases occur most often in adults and may be primary (nearly always in women) or secondary. Familial cases usually first manifest in childhood and are most often autosomal dominant. Secondary type 1 RTA may result from various disorders, drugs, or kidney transplantation:

• Autoimmune disease with hypergamma-globulinemia, particularly Sjogren's syndrome or RA

• Kidney transplantation

• Nephrocalcinosis

• Medullary sponge kidney

• Chronic obstructive uropathy

[**Table 237-1.** Some Features of Different Types of Renal Tubular Acidosis*]

• Drugs (mainly amphotericin B, ifosfamide, and lithium)

• Cirrhosis

• Sickle cell anemia

K level may be high with chronic obstructive uropathy or sickle cell anemia.

Type 2 (proximal) RTA: Type 2 is impairment in HCO_3 resorption in the proximal tubules, producing a urine pH > 7 if plasma HCO_3 concentration is normal, and a urine pH < 5.5 if plasma HCO_3 concentration is already depleted from ongoing losses. This syndrome may occur as part of a generalized dysfunction of proximal tubules and can be associated with increased urinary excretion of glucose, uric acid, phosphate, amino acids, citrate, Ca, K, and protein. Osteomalacia or osteopenia (including rickets in children) may develop. Mechanisms may include hypercalciuria, hyperphosphaturia, alterations in vitamin D metabolism, and secondary hyperparathyroidism. Type 2 RTA is very rare and most often occurs in patients who have one of the following:

• Fanconi syndrome

• Light chain nephropathy due to multiple myeloma

• Various drug exposures (usually acetazolamide, sulfonamides, ifosfamide, outdated tetracycline, or streptozocin)

It sometimes has other etiologies, including vitamin D deficiency, chronic hypocalcemia with secondary hyperparathyroidism, kidney transplantation, heavy metal exposure, and other inherited diseases (eg, fructose intolerance, Wilson's disease, oculocerebrorenal syndrome [Lowe syndrome], cystinosis).

Type 4 (generalized) RTA: Type 4 results from aldosterone deficiency or unresponsiveness of the distal tubule to aldosterone. Because aldosterone triggers Na resorption in exchange for K and hydrogen, there is reduced K excretion, causing hyperkalemia, and reduced acid excretion. Hyperkalemia may decrease ammonia excretion, contributing to metabolic acidosis. Urine pH is usually appropriate for serum pH (usually < 5.5 when there is serum acidosis). Plasma HCO_3 is usually > 17 mEq/L. This disorder is the most common type of RTA. It typically occurs sporadically secondary to impairment in the reninaldosterone-renal tubule axis (hyporeninemic hypoaldosteronism), which occurs in patients with the following:

• Diabetic nephropathy

• Chronic interstitial nephritis

Other factors that can contribute to type 4 RTA include the following:

• ACE inhibitor use

• Aldosterone synthase type I or II deficiency

• Angiotensin II receptor blocker use

• Chronic kidney disease, usually due to diabetic nephropathy or chronic interstitial nephritis

• Congenital adrenal hyperplasia, particularly 21-hydroxylase deficiency

• Critical illness

• Cyclosporine use

• Heparin use (including low molecular weight heparins)

• HIV nephropathy (due, possibly in part, to infection with *Mycobacterium avium* complex or cytomegalovirus)

• Interstitial renal damage (eg, due to SLE, obstructive uropathy, or sickle cell disease)

• K-sparing diuretics (eg, amiloride, eplere-none, spironolactone, triamterene)

• NSAID use

• Obstructive uropathy

• Other drugs (eg, pentamidine, trimethoprim)

• Primary adrenal insufficiency

• Pseudohypoaldosteronism (type I or II)

• Volume expansion (eg, in acute glomerulonephritis or chronic kidney disease)

Symptoms and Signs

RTA is usually asymptomatic. However, bony involvement (eg, bone pain and osteomalacia in adults and rickets in children) may occur in type 2 and sometimes in type 1 RTA. Nephrolithiasis and

nephrocalcinosis are possible, particularly with type 1 RTA.

Severe electrolyte disturbances are rare but can be life threatening. People with type 1 or type 2 RTA may show symptoms and signs of hypokalemia, including muscle weakness, hyporeflexia, and paralysis. Type 4 RTA is usually asymptomatic with only mild acidosis, but cardiac arrhythmias or paralysis may develop if hyperkalemia is severe. Signs of ECF volume depletion may develop from urinary water loss accompanying electrolyte excretion in type 2 RTA.

Diagnosis

• Suspected in patients with metabolic acidosis with normal anion gap or with unexplained hyperkalemia

• Serum and urine pH, electrolyte levels, and osmolalities

• Often, testing after stimulation (eg, with ammonium Cl, HCO_3, or a loop diuretic)

RTA is suspected in any patient with unexplained metabolic acidosis (low plasma HCO_3 and low blood pH) with normal anion gap. Type 4 RTA should be suspected in patients who have persistent hyperkalemia with no obvious cause, such as K supplements, K-sparing diuretics, or chronic kidney disease. ABG sampling is done to help confirm RTA and to exclude respiratory alkalosis as a cause of compensatory metabolic acidosis. Serum electrolytes, BUN, creatinine, and urine pH are measured in all patients. Further tests and sometimes provocative tests are done, depending on which type of RTA is suspected:

• **Type 1 RTA** is confirmed by a urine pH that remains > 5.5 during systemic acidosis. The acidosis may occur spontaneously or be induced by an acid load test (administration of ammonium Cl, 100 mg/kg po). Normal kidneys reduce urine pH to < 5.2 within 6 h of acidosis.

• **Type 2 RTA** is diagnosed by measurement of the urine pH and fractional HCO_3 excretion during an HCO_3 infusion ($NaHCO_3$, 0.5 to 1.0 mEq/kg/h IV). In type 2, urine pH rises above 7.5, and the fractional excretion of HCO_3 is > 15%. Because IV HCO_3 can contribute to hypokalemia, K supplements should be given in adequate amounts before infusion.

• **Type 4 RTA** is confirmed by a transtubular K concentration gradient of < 5 (normal value > 10), which indicates inappropriately low urinary K excretion, suggesting hypoaldosteronism or tubular unresponsiveness to aldosterone. The gradient is calculated by

$$\text{Transtubular K gradient} = \frac{\text{Urine K/Plasma K}}{\text{Urine osmolality/Plasma osmolaltiy}}$$

Definitive diagnosis can be obtained by measuring plasma renin and aldosterone levels after provocation (eg, administering a loop diuretic and having the patient remain upright for 3 h) but is usually not necessary.

Treatment

• Varies by type

• Often alkali therapy

• Treatment of concomitant abnormalities related to K, Ca, and phosphate metabolism

Treatment consists of correction of pH and electrolyte balance with alkali therapy. Failure to treat RTA in children slows growth.

Alkaline agents such as $NaHCO_3$ or Na citrate help achieve a relatively normal plasma HCO_3

concentration (22 to 24 mEq/L). K citrate can be substituted when persistent hypokalemia is present or, because Na increases Ca excretion, when Ca calculi are present. Vitamin D (eg, ergocalciferol, 800 IU po once/day) and oral Ca supplements (Ca carbonate, 1250 mg or 500 mg elemental Ca^{2+} tid) may also be needed to help reduce skeletal deformities resulting from osteomalacia or rickets.

Type 1 RTA: Adults are given $NaHCO_3$ or Na citrate (0.25 to 0.5 mEq/kg po q 6 h). In children, the total daily dose may need to be as much as 2 mEq/kg q 8 h; this dose can be adjusted as the child grows.

Type 2 RTA: Plasma HCO_3 cannot be restored to the normal range, but HCO_3 replacement should exceed the acid load of the diet (eg, $NaHCO_3$, 1 mEq/kg po q 6 h in adults or 2 to 4 mEq/kg q 6 h in children) to maintain serum HCO_3 at about 22 to 24 mEq/L because lower levels risk growth disturbance. However, excess HCO_3 replacement increases $KHCO_3$ losses in the urine. Thus, citrate salts can be substituted for $NaHCO_3$ and may be better tolerated.

K supplements or K citrate may be required in patients who become hypokalemic when given $NaHCO_3$ but is not recommended in patients with normal or high serum K levels. In difficult cases, treatment with low-dose hydrochlorothiazide (25 mg po bid) may stimulate proximal tubule transport functions. In cases of generalized proximal tubule disorder, hypophosphatemia and bone disorders are treated with phosphate and vitamin D supplementation to normalize the plasma phosphate concentration.

Type 4 RTA: Hyperkalemia is treated with volume expansion, dietary K restriction, and K-wasting diuretics (eg, furosemide 20 to 40 mg po once/day or bid titrated to effect). Alkalinization is often unnecessary. A few patients need mineralocorticoid replacement therapy (fludrocortisone, 0.1 to 0.2 mg po once/day, often higher in hyporeninemic hypoaldosteronism); mineralocorticoid replacement should be used with caution, because it may exacerbate underlying hypertension, heart failure, or edema.

Chapter 238. Renovascular Disorders

Introduction

(See also Renovascular Hypertension on p. 2077.)

Vascular disorders of the kidneys may involve partial or complete occlusion of large, medium, or small renal vessels and most commonly affect the glomeruli (see p. 2387). Systemic vasculitis (see p. 312) also may affect glomeruli.

Benign Hypertensive Arteriolar Nephrosclerosis

Benign hypertensive arteriolar nephrosclerosis is progressive renal impairment caused by chronic, poorly controlled hypertension. Symptoms and signs of chronic kidney disease may develop (eg, anorexia, nausea, vomiting, pruritus, somnolence or confusion), as may signs of end-organ damage secondary to hypertension. Diagnosis is primarily clinical, supported by routine laboratory test findings. Treatment is strict BP control and support of renal function.

Benign hypertensive arteriolar nephrosclerosis results when chronic hypertension damages small blood vessels, glomeruli, renal tubules, and interstitial tissues. As a result, progressive chronic kidney disease develops.

Benign nephrosclerosis progresses to end-stage renal disease in only a small percentage of patients. However, because chronic hypertension and benign nephrosclerosis are common, benign nephrosclerosis is one of the most common diagnoses in patients with end-stage renal disease. It is termed benign to distinguish it from malignant arteriolar nephrosclerosis, which is a synonym for hypertensive emergency (see p. 2078).

Risk factors include older age, poorly controlled moderate to severe hypertension, and other renal disorders (eg, diabetic nephropathy). Blacks are at increased risk; it is unclear if the risk is increased because poorly treated hypertension is more common among blacks or because blacks are more genetically susceptible to hypertension-induced renal damage.

Symptoms and Signs

Symptoms and signs of chronic kidney disease, such as anorexia, nausea, vomiting, pruritus, somnolence or confusion, weight loss, and an unpleasant taste in the mouth, may develop (see p. 2443). Signs of hypertension-related end-organ damage may occur in the vasculature of the eyes and in the skin, CNS, and periphery.

Diagnosis

• History of hypertension

• Blood tests indicating renal failure

• Signs of hypertensive end-organ damage

• No other cause of chronic kidney disease

The diagnosis may be suspected when routine blood tests indicate deteriorating renal function (eg, elevated creatinine and BUN, hyperphosphatemia) in a hypertensive patient. Diagnosis is usually inferred because of the history and evidence of hypertension-related end-organ damage (eg, retinal changes, left ventricular hypertrophy) on physical examination. Hypertension should be present before onset of proteinuria and renal failure, and there should be no other clinically suspected cause of renal failure.

Urine testing should not suggest other causes of renal failure (eg, glomerulonephritis or hypertensive emergency). On urinalysis, there should be few cells or casts in the sediment, and protein excretion is

usually < 1 g/day (it is occasionally higher and in the nephrotic range).

Ultrasonography is done only if other causes of renal failure must be excluded. It may show that kidney size is reduced. Renal biopsy is done only if the diagnosis remains unclear.

Prognosis

Prognosis usually depends on adequacy of BP control and degree of renal failure. Usually, renal impairment progresses slowly; after 5 to 10 yr, only 1 to 2% of patients develop clinically significant renal dysfunction.

Treatment

• BP control

Treatment involves strict BP control (see p. 2069). The BP goal is < 140/90 mm Hg, although < 130/80 mm Hg is more appropriate for patients with diabetes or chronic kidney disease. Most experts suggest low-dose thiazide diuretic therapy. Among patients with proteinuria, an ACE inhibitor or angiotensin II receptor blocker is added. Ca channel blockers and β-blockers can be added as needed; most patients require combination therapy for BP control. Weight loss, exercise, and salt and water restriction also help control BP. Chronic renal failure should be managed (see p. 2444).

Renal Artery Stenosis and Occlusion

Renal artery stenosis is a decrease in blood flow through one or both of the main renal arteries or their branches. Renal artery occlusion is a complete blockage of blood flow through one or both of the main renal arteries or its branches. Stenosis and occlusion are usually due to thromboemboli, atherosclerosis, or fibromuscular dysplasia. Symptoms of acute occlusion include steady, aching flank pain, abdominal pain, fever, nausea, vomiting, and hematuria. Acute renal failure may develop. Chronic, progressive stenosis causes refractory hypertension and may lead to chronic kidney disease. Diagnosis is by imaging tests (eg, CT angiography, magnetic resonance angiography). Treatment of acute occlusion is with anticoagulation and sometimes fibrinolytics and surgical or catheter-based embolectomy, or a combination. Treatment of chronic, progressive stenosis includes angioplasty with stenting, surgical bypass, and removal of an infarcted kidney.

Renal hypoperfusion results in hypertension (see Renovascular Hypertension on p. 2077), renal failure, and, if complete occlusion occurs, renal infarction and necrosis.

Etiology

Occlusion may be acute or chronic. Acute occlusion is usually unilateral. Chronic occlusion may be unilateral or bilateral.

Acute occlusion: The most common cause is thromboembolism. Emboli may originate in the heart (due to atrial fibrillation, after MI, or from vegetations due to bacterial endocarditis) or the aorta (as atheroemboli); less often, fat or tumor emboli are the cause. Thrombosis may occur in a renal artery spontaneously or after trauma, surgery, angiography, or angioplasty. Other causes of acute occlusion include dissection or rupture of a renal artery aneurysm.

Rapid, total occlusion of large renal arteries for 30 to 60 min results in infarction. The infarct is typically wedge-shaped, radiating outward from the affected vessel.

Chronic progressive stenosis: About 90% of cases are due to atherosclerosis, which is usually bilateral. Almost 10% of cases are due to fibromuscular dysplasia (FMD), which is commonly unilateral. Less than 1% of cases result from Takayasu's arteritis, Kawasaki disease, neurofibromatosis type 1, aortic wall hematoma, or aortic dissection.

Atherosclerosis develops primarily in patients > 50 (more often men) and usually affects the aortic orifice or proximal segment of the renal artery. Chronic progressive stenosis tends to become clinically evident after about 10 yr of atherosclerosis, causing renal atrophy and chronic kidney disease.

FMD is pathologic thickening of the arterial wall, most often of the distal main renal artery or the intrarenal branches. This disorder develops primarily in younger adults, particularly in women aged 20 to 50. It is more common among 1st-degree relatives of patients with FMD and among people with the *ACE1* gene.

Symptoms and Signs

Manifestations depend on rapidity of onset, extent, whether unilateral or bilateral, and duration of renal hypoperfusion. Stenosis of one renal artery is often asymptomatic for a considerable time.

Acute complete occlusion of one or both renal arteries causes steady and aching flank pain, abdominal pain, fever, nausea, and vomiting. Gross hematuria, oliguria, or anuria may occur; hypertension is rare. After 24 h, symptoms and signs of acute renal failure may develop (see p. 2438). If the cause was thromboembolic, features of thromboembolism at other sites (eg, blue toes, livedo reticularis, retinal lesions on funduscopic examination) also may be present.

Chronic progressive stenosis causes hypertension, which may begin at an atypical age (eg, < 30 yr or after age 50 yr) and which may be refractory to control despite use of multiple antihypertensives. Physical examination may detect an abdominal bruit or signs of atherosclerosis. Symptoms and signs of chronic kidney disease (see p. 2443) develop slowly.

Diagnosis

• Clinical suspicion

• Imaging

Diagnosis is suspected in patients with renal failure and who have

• Symptoms of acute renal artery occlusion

• Symptoms or signs of thromboembolism

• Hypertension that begins before age 30 or is refractory to treatment with > 3 antihypertensive drugs

Blood and urine tests are done to confirm renal failure. Diagnosis is confirmed by imaging tests (see Table 238-1). Which tests are done depends on the patient's renal function and other characteristics and on test availability.

Some tests (CT angiography, arteriography, digital subtraction angiography) require an IV ionic radiocontrast agent, which may be nephrotoxic; this risk is lower with the nonionic hypo-osmolar or iso-osmolar contrast agents that are now in widespread use (see p. 3403). Magnetic resonance angiography (MRA) requires the use of gadolinium contrast; in patients with severe chronic kidney disease, gadolinium contrast carries the risk of nephrogenic systemic fibrosis, a condition that closely resembles systemic sclerosis and that has no satisfactory method of treatment.

When results of other tests are inconclusive or negative but clinical suspicion is strong, arteriography is necessary for definitive diagnosis. Arteriography may also be needed before invasive interventions.

When a thromboembolic disorder is suspected, ECG (to detect atrial fibrillation) and hypercoagulability studies may be needed to identify treatable embolic sources. Transesophageal echocardiography is done to detect atheromatous lesions in the ascending and thoracic aorta and cardiac sources of thrombi or valvular vegetations.

Blood and urine tests are nondiagnostic but are done to confirm renal failure, indicated by elevated creatinine and BUN and by hyperkalemia. Leukocytosis, gross or microscopic hematuria, and proteinuria may also be present.

Treatment

- Restoration of vascular patency in acute occlusions and, if patients have refractory hypertension or potential for renal failure, in chronic stenosis

Treatment depends on the cause.

Acute renal artery occlusion: A renal thromboembolic disorder may be treated with a combination of anticoagulation, fibrinolytics, and surgical or catheter-based embolectomy. Treatment within 3 h of symptom onset is likely to improve renal function. However, complete recovery is unusual, and early and

[**Table 238-1.** Imaging Tests for Diagnosis of Renal Artery Stenosis or Occlusion]

late mortality rates are high because of extrarenal embolization or underlying atherosclerotic heart disease.

Patients presenting within 3 h may benefit from fibrinolytic (thrombolytic) therapy (eg, streptokinase, alteplase) given IV or by local intra-arterial infusion (see p. 2110). However, such rapid diagnosis and treatment is rare.

All patients with a thromboembolic disorder require anticoagulation with IV heparin, unless contraindicated. Long-term anticoagulation with oral warfarin can be initiated simultaneously with heparin if no invasive intervention is planned. Anticoagulation should be continued for at least 6 to 12 mo —indefinitely for patients with a recurrent thromboembolic disorder or a hypercoagulability disorder.

Surgery to restore vascular patency has a higher mortality rate than fibrinolytic therapy and has no advantage in recovery of renal function. However, surgery, particularly if done within the first few hours, is preferred for patients with traumatic renal artery thrombosis. If patients with nontraumatic, severe renal failure do not recover function after 4 to 6 wk of drug therapy, surgical revascularization (embolectomy) can be considered, but it helps only a few.

If the cause is thromboemboli, the source should be identified and treated appropriately (see Deep Venous Thrombosis on p. 2224).

Chronic progressive renal artery stenosis: Treatment is indicated when > 75% of the arterial diameter is blocked (stenosis) and patients have any of the following:

- Unilateral stenosis with renal insufficiency

- Bilateral stenoses

- Stenosis in a solitary functioning kidney

- Unilateral or bilateral stenosis associated with hypertension that is refractory to treatment with ≥ 3 drugs

Treatment is with percutaneous transluminal angioplasty (PTA) plus stenting or with surgical bypass of the stenotic segment. Usually, an extensively infarcted kidney must be removed if revascularization is not expected to result in functional recovery. Surgery is usually more effective than PTA for atherosclerotic occlusion; it cures or attenuates hypertension in 60 to 70% of patients. PTA is preferred for FMD; risk is minimal, success rate is high, and restenosis rate is low. If PTA is ineffective, surgical revascularization is needed.

Renovascular hypertension: Treatments are typically ineffective unless vascular patency (see p. 2077) is restored. ACE inhibitors, angiotensin II receptor blockers, or renin inhibitors can be used in unilateral

but not in bilateral renal artery stenosis. These drugs can reduce GFR and increase serum BUN and creatinine levels. If GFR decreases enough to increase serum creatinine, Ca channel blockers (eg, amlodipine, felodipine) or vasodilators (eg, hydralazine, minoxidil) should be added or substituted (see p. 2071).

Renal Atheroembolism

Renal atheroembolism is occlusion of renal arterioles by atherosclerotic emboli, causing progressive chronic kidney disease. It results from rupture of atheromatous plaques. Symptoms are those of renal failure; symptoms and signs of widespread arterial embolic disease may be present. Diagnosis is by renal biopsy. Long-term prognosis is usually poor. Treatment aims to prevent further embolization.

Atheromatous plaque rupture usually results from manipulation of the aorta during vascular surgery, angioplasty, or arteriography. Spontaneous plaque rupture, which occurs most often in patients who have diffuse erosive atherosclerosis or who are being treated with anticoagulants or fibrinolytics, is rare.

Atheroemboli tend to cause incomplete occlusion with secondary ischemic atrophy rather than renal infarction. A foreign body immune reaction often follows embolization, leading to continued deterioration in renal function for 3 to 8 wk. Acute renal impairment may also result from massive or recurrent episodes of embolization.

Symptoms and Signs

Symptoms are usually those of acute or chronic renal dysfunction with uremia (see p. 2438). Renal atheroembolism rarely causes hypertension. Abdominal pain, nausea, and vomiting can result from concomitant compromised arterial microcirculation of abdominal organs (eg, pancreas, GI tract). Sudden blindness and formation of bright yellow retinal plaques (Hollenhorst plaques) can result from emboli in retinal arterioles. Signs of widespread peripheral embolism (eg, livedo reticularis, painful muscle nodules, overt gangrene, which is often referred to as the trash syndrome, are sometimes present.

Diagnosis

• Clinical suspicion

• Imaging (usually renal ultrasonography)

• Sometimes, renal biopsy

• Location of source of emboli

Diagnosis is suggested by worsening renal function in a patient with recent manipulation of the aorta, particularly if there are signs of atheroemboli. Differential diagnosis includes contrast-induced and drug-induced nephropathy. An imaging study (usually ultrasonography) should be done. If suspicion of atheroembolism remains high, percutaneous renal biopsy is done; it has a sensitivity of about 75%. Diagnosis is important because there may be treatable causes of emboli in the absence of vascular obstruction. Cholesterol crystals in the emboli dissolve during tissue fixation, leaving pathognomonic biconcave, needle-shaped clefts in the occluded vessel. Sometimes skin, muscle, or GI biopsy can provide the same information and indirectly help establish the diagnosis.

Blood and urine tests can confirm the diagnosis of acute renal failure or chronic kidney disease but do not establish cause. Urinalysis typically shows microscopic hematuria and minimal proteinuria; however, proteinuria is occasionally in the nephrotic range (> 3 g/day). Eosinophilia, eosinophiluria, and transient hypocomplementemia may be present.

If renal or systemic emboli recur and their source is unclear, transesophageal echocardiography is done to detect atheromatous lesions in the ascending and thoracic aorta and cardiac sources of emboli; dual helical CT may help characterize the ascending aorta and aortic arch.

Prognosis

With aggressive supportive therapy, survival has improved in recent years (eg, survival can be > 50% at 4 yr). Some patients require renal replacement therapy initially, but they improve later and dialysis may be stopped.

Treatment

• Treatment of embolic source when possible

• Supportive measures

• Modification of risk factors

Sometimes the source of emboli can be treated (eg, anticoagulation for patients with emboli from a cardiac source and atrial fibrillation and for patients in whom a clot becomes a source of new emboli). However, no direct treatment of existing renal emboli is effective. Corticosteroids, antiplatelet drugs, vasodilators, and plasma exchange are not helpful. There is no demonstrated benefit of anticoagulation, and, according to most experts, its use may actually enhance atheroembolism.

Treatment of renal dysfunction includes control of hypertension and management of electrolytes and fluid status; sometimes dialysis is required. Modifying risk factors for atherosclerosis may slow its progression and induce regression. Strategies include management of hypertension, hyperlipidemia, and diabetes; smoking cessation; and encouragement of regular aerobic exercise and good nutrition (see p. 2084).

Renal Cortical Necrosis

Renal cortical necrosis is destruction of cortical tissue resulting from renal arteriolar injury and leading to chronic kidney disease. This rare disorder typically occurs in neonates and in pregnant or postpartum women when sepsis or pregnancy complications occur. Symptoms and signs include gross hematuria, flank pain, decreased urine output, fever, and symptoms of uremia. Symptoms of the underlying disorder may predominate. Diagnosis is by MRI, CT, isotopic renal scanning, or renal biopsy. Mortality rate at 1 yr is > 20%. Treatment is directed at the underlying disorder and at preserving renal function.

In renal cortical necrosis, which may be patchy or diffuse, bilateral renal arteriolar injury results in destruction of cortical tissues and acute renal failure. Renal cortical tissues eventually calcify. The juxtamedullary cortex, medulla, and the area just under the capsule are spared.

Etiology

Injury usually results from reduced renal artery perfusion secondary to vascular spasm, microvascular injury, or intravascular coagulation.

About 10% of cases occur in infants and children. Pregnancy complications increase risk of this disorder in neonates and in women, as does sepsis. Other causes (eg, disseminated intravascular coagulation [DIC]) are less common (see Table 238-2).

Symptoms and Signs

Gross hematuria, flank pain, and sometimes decreased urine output or abrupt anuria occur. Fever is common, and chronic kidney disease with hypertension develops. However, these symptoms are often overshadowed by symptoms of the underlying disorder.

Diagnosis

• Imaging, usually with CT angiography

[Table 238-2. Causes of Renal Cortical Necrosis]

Diagnosis is suspected when typical symptoms occur in patients with a potential cause.

Imaging tests can sometimes confirm the diagnosis. CT angiography is usually preferred despite the risks of using an iodinated contrast agent. Because of the risk of nephrogenic systemic fibrosis, use of magnetic resonance angiography with gadolinium contrast is not recommended in these patients, who usually have severe renal dysfunction.

An alternative is isotopic renal scanning using diethylenetriamine penta-acetic acid. It shows enlarged, nonobstructed kidneys, with little or no renal blood flow. Renal biopsy is done only if the diagnosis is unclear and no contraindications exist. It provides definitive diagnosis and prognostic information.

Urinalysis, CBC, liver function tests, and serum electrolytes and renal function tests are done routinely. These tests often confirm renal dysfunction (eg, indicated by elevated creatinine and BUN and by hyperkalemia) and may suggest a cause. Severe electrolyte abnormalities may be present depending on the cause (eg, hyperkalemia, hyperphosphatemia, hypocalcemia). CBC often detects leukocytosis (even when sepsis is not the cause) and may detect anemia and thrombocytopenia if hemolysis, DIC, or sepsis is the cause. Transaminases may be increased in relative hypovolemic states (eg, septic shock, postpartum hemorrhage). If DIC is suspected, coagulation studies are done. They may detect low fibrinogen levels, increased fibrin-degradation products, and increasing PT/INR and PTT. Urinalysis typically detects proteinuria and hematuria.

Prognosis

Prognosis of renal cortical necrosis was poor in the past, with mortality > 50% in the first year. More recently, with aggressive supportive therapy, 1-yr mortality can be about 20%, and up to 20% of survivors may recover some renal function.

Treatment

Treatment is directed at the underlying disorder and at preserving renal function (eg, with early dialysis).

Renal Vein Thrombosis

Renal vein thrombosis is thrombotic occlusion of one or both main renal veins, resulting in acute renal failure or chronic kidney disease. Common causes include nephrotic syndrome, primary hypercoagulability disorders, malignant renal tumors, extrinsic compression, trauma, and rarely inflammatory bowel disease. Symptoms of renal failure and sometimes nausea, vomiting, flank pain, gross hematuria, decreased urine output, or systemic manifestations of venous thromboembolism may occur. Diagnosis is by CT, magnetic resonance angiography, or renal venography. With treatment, prognosis is generally good. Treatment is anticoagulation, support of renal function, and treatment of the underlying disorder. Some patients benefit from thrombectomy or nephrectomy.

Etiology

Renal vein thrombosis usually results from local and systemic hypercoagulability due to nephrotic syndrome associated with membranous nephropathy or membranoproliferative glomerulonephritis. Overly aggressive diuresis or prolonged high-dose corticosteroid treatment may contribute to thrombosis of the renal vein in patients with these conditions (see p. 2408). Other causes include

• Allograft rejection

• Amyloidosis

- Diabetic nephropathy
- Estrogen therapy
- Pregnancy
- Primary hypercoagulability disorders (eg, antithrombin III deficiency, protein C or S deficiency, factor V Leiden, prothrombin G20210A mutations)
- Renal vasculitis
- Sickle cell nephropathy
- SLE

Less common causes are related to reduced renal vein blood flow and include malignant renal tumors that extend into the renal veins (typically renal cell carcinoma), extrinsic compression of the renal vein or inferior vena cava (eg, by vascular abnormalities, tumor, retroperitoneal disease, ligation of the inferior vena cava, aortic aneurysm), oral contraceptive use, trauma, dehydration, and, rarely, thrombophlebitis migrans and cocaine abuse.

Symptoms and Signs

Usually, onset of renal dysfunction (see p. 2436) is insidious. However, onset may be acute, causing renal infarction with nausea, vomiting, flank pain, gross hematuria, and decreased urine output.

When the cause is a hypercoagulability disorder, signs of venous thromboembolic disorders (eg, deep venous thrombosis, pulmonary embolism) may occur. When the cause is a renal cancer, its signs (eg, hematuria, weight loss) predominate.

Diagnosis

- Vascular imaging

Renal vein thrombosis should be considered in patients with renal infarction or any unexplained deterioration in renal function, particularly in patients with the nephrotic syndrome or other risk factors. The traditional diagnostic test of choice and the gold standard is venography of the inferior vena cava; this test is diagnostic, but it may mobilize clots. Because of the risks of conventional venography, magnetic resonance venography and Doppler ultrasonography are being used increasingly. Magnetic resonance venography can be done if GFR > 30 mL/min. Doppler ultrasonography sometimes detects renal vein thrombosis but has high false-negative and false-positive rates. Notching of the ureter due to dilated collateral veins is a characteristic finding in some chronic cases. CT angiography provides good detail with high sensitivity and specificity and is fast but requires administration of a radiocontrast agent, which may be nephrotoxic. Serum electrolytes and urinalysis are done and confirm deterioration of renal function. Microscopic hematuria is often present. Proteinuria may be in the nephrotic range.

If no cause is apparent, testing for hypercoagulability disorders should be initiated (see p. 973). Renal biopsy is nonspecific but may detect a coexisting renal disorder.

Treatment

- Treatment of underlying disorder
- Anticoagulation
- Sometimes percutaneous catheter-directed thrombectomy or thrombolysis

Death is rare and usually related to complications such as pulmonary embolism and those due to

nephrotic syndrome or a malignant tumor.

The underlying disorder should be treated. Treatment options for renal vein thrombosis include anticoagulation with heparin, thrombolysis, and catheter-directed or surgical thrombectomy. Long-term anticoagulation with low molecular weight heparin or oral warfarin should be started immediately if no invasive intervention is planned. Anticoagulation minimizes risk of new thrombi, promotes recanalization of vessels with existing clots, and improves renal function. Anticoagulation should be continued for at least 6 to 12 mo and, if a hypercoagulability disorder (eg, persistent nephrotic syndrome) is present, indefinitely.

Use of a percutaneous catheter for thrombectomy or thrombolysis is a promising new technique that has a high success rate. Surgical thrombectomy is rarely used but may help if anticoagulation is ineffective or contraindicated. Inferior vena cava filters may also be used in these cases to help prevent pulmonary emboli.

Nephrectomy is done only if infarction is total (in certain cases) or if the underlying disorder warrants it.

Chapter 239. Renal Failure

Introduction

Renal failure is traditionally categorized as acute or chronic. The former develops rapidly, often over days, whereas the latter progresses slowly over months to years. Some causes overlap.

Acute Renal Failure

(Acute Kidney Injury)

Acute renal failure (ARF) is a rapid decrease in renal function over days to weeks, causing an accumulation of nitrogenous products in the blood (azotemia). It often results from severe trauma, illness, or surgery but is sometimes caused by a rapidly progressive, intrinsic renal disease. Symptoms include anorexia, nausea, and vomiting. Seizures and coma may occur if the condition is untreated. Fluid, electrolyte, and acid-base disorders develop quickly. Diagnosis is based on laboratory tests of renal function, including serum creatinine. Urinary indices, urinary sediment examination, and often imaging and other tests are needed to determine the cause. Treatment is directed at the cause but also includes fluid and electrolyte management and sometimes dialysis.

In all cases of ARF, creatinine and urea build up in the blood over several days, and fluid and electrolyte disorders develop. The most serious of these disorders are hyperkalemia and fluid overload (possibly causing pulmonary edema). Phosphate retention leads to hyperphosphatemia. Hypocalcemia is thought to occur because the impaired kidney no longer produces calcitriol and because hyperphosphatemia causes Ca phosphate precipitation in the tissues. Acidosis develops because hydrogen ions cannot be excreted. With significant uremia, coagulation may be impaired, and pericarditis may develop. Urine output varies with the type and cause of ARF.

Etiology

Causes of ARF can be classified as prerenal, renal, or postrenal (see Table 239-1).

Prerenal azotemia is due to inadequate renal perfusion. The main causes are ECF volume depletion and cardiovascular disease. Prerenal conditions cause about 50 to 80% of ARF but do not cause permanent renal damage (and hence are potentially reversible) unless hypoperfusion is severe enough to cause tubular ischemia. Hypoperfusion of an otherwise functioning kidney leads to enhanced reabsorption of Na and water, resulting in oliguria with high urine osmolality and low urine Na.

Renal causes of ARF involve intrinsic renal disease or damage. Renal causes are responsible for about 10 to 40% of cases. Overall, the most common causes are prolonged renal ischemia and nephrotoxins (including IV use of iodinated radiopaque contrast agents—see Contrast Nephropathy on p. 2414). Disorders may involve the glomeruli, tubules, or interstitium. Glomerular disease reduces GFR and increases glomerular capillary permeability to proteins; it may be inflammatory (glomerulonephritis) or the result of vascular damage from ischemia or vasculitis. Tubules also may be damaged by ischemia and may become obstructed by cellular debris, protein or crystal deposition, and cellular or interstitial edema. Tubular damage impairs reabsorption of Na, so urinary Na tends to be elevated, which is helpful diagnostically. Interstitial inflammation (nephritis) usually involves an immunologic or allergic phenomenon. These mechanisms of tubular damage are complex and interdependent, rendering the previously popular term acute tubular necrosis an inadequate description.

Postrenal azotemia (obstructive nephropathy—see also p. 2365) is due to various types of obstruction in the voiding and collecting parts of the urinary system and is responsible for about 5 to 10% of cases. Obstruction can also occur within the tubules when crystalline or proteinaceous material precipitates. This form of renal failure is often grouped with postrenal failure because the mechanism is obstructive. Obstructed ultrafiltrate flow in tubules or more distally increases pressure in the urinary space of the glomerulus, reducing GFR. Obstruction also affects renal blood flow, initially increasing the flow and

pressure in the glomerular capillary by reducing afferent arteriolar resistance. However, within 3 to 4 h, the renal blood flow is reduced, and by 24 h, it has fallen to < 50% of normal because of increased resistance of renal vasculature. Renovascular resistance may take up to a week to return to normal after relief of a 24-h obstruction. To produce significant azotemia, obstruction at the level of the ureter requires involvement of both ureters unless the patient has only a single functioning kidney. Bladder

[Table 239-1. Major Causes of Acute Renal Failure]

outlet obstruction is probably the most common cause of sudden, and often total, cessation of urinary output in men.

Urine output: Prerenal causes typically manifest with oliguria, not anuria. Anuria usually occurs only in obstructive uropathy or, less commonly, in bilateral renal artery occlusion, acute cortical necrosis, or rapidly progressive glomerulonephritis.

A relatively preserved urine output of 1 to 2.4 L/day is initially present in most renal causes. In acute tubular injury, output may have 3 phases.

- The **prodromal phase**, with usually normal urine output, varies in duration depending on causative factors (eg, the amount of toxin ingested, the duration and severity of hypotension).

- The **oliguric phase**, with output typically between 50 and 400 mL/day, lasts an average of 10 to 14 days but varies from 1 day to 8 wk. However, many patients are never oliguric. Nonoliguric patients have lower mortality and morbidity and less need for dialysis.

- In the **postoliguric phase**, urine output gradually returns to normal, but serum creatinine and urea levels may not fall for several more days. Tubular dysfunction may persist and is manifested by Na wasting, polyuria (possibly massive) unresponsive to vasopressin, or hyperchloremic metabolic acidosis.

Symptoms and Signs

Initially, weight gain and peripheral edema may be the only findings. Often, predominant symptoms are those of the underlying illness or those caused by the surgical complication that precipitated renal deterioration. Later, as nitrogenous products accumulate, symptoms of uremia may develop, including anorexia, nausea and vomiting, weakness, myoclonic jerks, seizures, confusion, and coma; asterixis and hyperreflexia may be present on examination. Chest pain (typically worse with inspiration or when recumbent), a pericardial friction rub, and findings of pericardial tamponade may occur if uremic pericarditis is present. Fluid accumulation in the lungs may cause dyspnea and crackles on auscultation.

Other findings depend on the cause. Urine may be cola-colored in glomerulonephritis or myoglobinuria. A palpable bladder may be present with outlet obstruction.

Diagnosis

- Serum creatinine

- Urinary sediment

- Urinary diagnostic indices

- Postvoid residual bladder volume if postrenal cause suspected

ARF is suspected when urine output falls or serum BUN and creatinine rise. Evaluation should determine the presence and type of ARF and seek a cause. Blood tests generally include CBC, BUN, creatinine, and electrolytes (including Ca and phosphate). Urine tests include Na and creatinine concentration and microscopic analysis of sediment. Early detection and treatment increase the chances of reversing renal failure.

A progressive daily rise in serum creatinine is diagnostic of ARF. Serum creatinine can increase by as much as 2 mg/dL/day (180 µmol/L/day), depending on the amount of creatinine produced (which varies with lean body mass) and total body water. A rise of > 2 mg/dL/day suggests overproduction due to rhabdomyolysis.

Urea nitrogen may increase by 10 to 20 mg/dL/day (3.6 to 7.1 mmol urea/L/day), but BUN may be misleading because it is frequently elevated in response to increased protein catabolism resulting from surgery, trauma, corticosteroids, burns, transfusion reactions, parenteral nutrition or GI or internal bleeding.

When creatinine is rising, 24-h urine collection for creatinine clearance and the various formulas used to calculate creatinine clearance from serum creatinine are inaccurate and should not be used in estimating GFR, because the rise in serum creatinine concentration is a delayed function of GFR decline.

Other laboratory findings are progressive acidosis, hyperkalemia, hyponatremia, and anemia. Acidosis is ordinarily moderate, with a plasma HCO_3 content of 15 to 20 mmol/L. Serum K concentration increases slowly, but when catabolism is markedly accelerated, it may rise by 1 to 2 mmol/L/day. Hyponatremia usually is moderate (serum Na, 125 to 135 mmol/L) and correlates with a surplus of water. Normochromic-normocytic anemia with an Hct of 25 to 30% is typical.

Hypocalcemia is common and may be profound in patients with myoglobinuric ARF, apparently because of the combined effects of Ca deposition in necrotic muscle, reduced calcitriol production, and resistance of bone to parathyroid hormone (PTH). During recovery from ARF, hypercalcemia may supervene as renal calcitriol production increases, the bone becomes responsive to PTH, and Ca deposits are mobilized from damaged tissue.

Determination of cause: Immediately reversible prerenal or postrenal causes must be excluded first. ECF volume depletion and obstruction are considered in all patients. The drug history must be accurately reviewed and all potentially renal toxic drugs stopped. Urinary diagnostic indices (see Table 239-2) are helpful in distinguishing prerenal azotemia from acute tubular injury, which are the most common causes of ARF in hospitalized patients.

Prerenal causes are often apparent clinically. If so, correction of an underlying hemodynamic abnormality (eg, with volume infusion) should be attempted. Abatement of ARF confirms a prerenal cause.

Postrenal causes should be sought in most cases of acute renal failure. Immediately after the patient voids, a urethral catheter is placed or bedside ultrasonography is used to determine the residual urine in the bladder. A postvoid residual urine volume > 200 mL suggests bladder outlet obstruction, although detrusor muscle weakness and neurogenic bladder may also cause residual volume of this amount. The catheter may be kept in for the first day to monitor hourly output but is removed once oliguria is confirmed (if bladder outlet obstruction is not present) to decrease risk of infection. Renal ultrasonography is then done to diagnose more proximal obstruction. However, sensitivity for obstruction is only 80 to 85% when ultrasonography is used because the collecting system is not always dilated, especially when the condition is acute, an intrarenal pelvis is present, the ureter is encased (eg, in retroperitoneal fibrosis or neoplasm), or the patient has concomitant hypovolemia. If obstruction is strongly suspected, CT can establish the site of obstruction and guide therapy.

The **urinary sediment** may provide etiologic clues. A normal urine sediment occurs in prerenal azotemia and sometimes in obstructive uropathy. With renal tubular injury, the sediment characteristically contains tubular cells, tubular cell casts, and many brown-pigmented granular casts. Urinary eosinophils suggest allergic tubulointerstitial nephritis. RBC casts indicate glomerulonephritis or vasculitis.

Renal causes are sometimes suggested by clinical findings. Patients with glomerulonephritis (see Ch. 235) often have edema, marked proteinuria (nephrotic syndrome), or signs of arteritis in the skin and retina, often without a history of intrinsic renal disease. Hemoptysis suggests Wegener's granulomatosis or Goodpasture's syndrome. Certain rashes (eg, erythema nodosum, cutaneous vasculitis, discoid lupus) suggest polyarteritis, cryoglobulinemia, SLE, or Henoch-Schonlein purpura. Tubulointerstitial nephritis

and drug allergy are suggested by a history of drug ingestion and a maculopapular or purpuric rash.

To further differentiate renal causes, antistreptolysin-O and complement titers, antinuclear antibodies, and antineutrophil cytoplasmic antibodies are determined. Renal biopsy may be done if the diagnosis remains elusive (see
Table 239-3).

Imaging: In addition to renal ultrasonography, other imaging tests are occasionally of use. In evaluating for ureteral obstruction, noncontrast CT is preferred over antegrade and retrograde urography. In addition to its ability to delineate soft-tissue structures and Ca-containing calculi, CT can detect nonradiopaque calculi.

Contrast agents should be avoided if possible. However, renal arteriography or venography may sometimes be indicated if vascular causes are suggested clinically. Magnetic resonance angiography was increasingly being

[**Table 239-2.** Urinary Diagnostic Indices in Prerenal Azotemia and Acute Tubular Injury]

[**Table 239-3.** Causes of Acute Renal Failure Based on Laboratory Findings]

used for diagnosing renal artery stenosis as well as thrombosis of both arteries and veins because MRI used gadolinium, which was thought to be safer than the iodinated contrast agents used in angiography and contrast-enhanced CT. However, recent evidence suggests that gadolinium may be involved in the pathogenesis of nephrogenic systemic fibrosis, a serious complication that occurs only in patients with renal failure. Thus, many experts recommend avoiding gadolinium in patients with renal failure.

Kidney size, as determined with imaging tests, is helpful to know, because a normal or enlarged kidney favors reversibility, whereas a small kidney suggests chronic renal insufficiency.

Prognosis

Although many causes are reversible if diagnosed and treated early, the overall survival rate remains about 50% because many patients with ARF have significant underlying disorders (eg, sepsis, respiratory failure). Death is usually the result of these disorders rather than the renal failure itself. Most survivors have adequate kidney function. About 10% require dialysis or transplantation—half right away and the others as renal function slowly deteriorates.

Treatment

- Immediate treatment of pulmonary edema and hyperkalemia
- Dialysis as needed to control hyperkalemia, pulmonary edema, metabolic acidosis, and uremic symptoms
- Adjustment of drug regimen
- Usually restriction of water, Na, and K intake, but provision of adequate protein
- Possibly phosphate binders and Na polystyrene sulfonate

Emergency treatment: Life-threatening complications are addressed, preferably in a critical care unit. Pulmonary edema (see p. 2131) is treated with O_2, IV vasodilators (eg, nitroglycerin), and diuretics (often ineffective in ARF). Hyperkalemia (see p. 835) is treated as needed with IV infusion of 10 mL of 10% Ca gluconate, 50 g of dextrose, and 5 to 10 units of insulin. These drugs do not reduce total body K, so further (but slower acting) treatment with 30 g of oral or rectal Na polystyrene sulfonate is begun. Although correction of an anion gap metabolic acidosis with $NaHCO_3$ is controversial, correction of the nonanion gap portion of severe metabolic acidosis (pH < 7.20) is less controversial. The nonanion gap

portion may be treated with IV $NaHCO_3$ in the form of a slow infusion (≤ 150 mEq $NaHCO_3$ in 1 L of 5% D/W at a rate of 50 to 100 mL/h). The nonanion gap portion of metabolic acidosis is determined by calculating the increase in anion gap above normal and then subtracting this number from the decrease in HCO_3 from 24 mmol/L. HCO_3 is given to raise the serum HCO_3 by this difference. Because variations in body buffer systems and the rate of acid production are hard to predict, calculating the amount of HCO_3 needed to achieve a full correction is usually not recommended. Instead, HCO_3 is given via continuous infusion and the anion gap is monitored serially.

Hemodialysis (see p. 2447) or **hemofiltration** (see p. 2449) is initiated when

- Severe electrolyte abnormalities cannot otherwise be controlled (eg, K > 6 mmol/L)
- Pulmonary edema persists despite drug treatment
- Metabolic acidosis is unresponsive to drug treatment
- Uremic symptoms occur (eg, vomiting thought to be due to uremia, asterixis, encephalopathy, pericarditis, seizures)

BUN and creatinine levels are probably not the best guides for initiating dialysis in ARF. In asymptomatic patients who are not seriously ill, particularly those in whom return of renal function is considered likely, dialysis can be deferred until symptoms occur, thus avoiding placement of a central venous catheter with its attendant complications.

General measures: Nephrotoxic drugs are stopped, and all drugs excreted by the kidneys (eg, digoxin, some antibiotics) are adjusted; serum levels are useful.

Daily water intake is restricted to a volume equal to the previous day's urine output plus measured extrarenal losses (eg, vomitus) plus 500 to 1000 mL/day for insensible loss. Water intake can be further restricted for hyponatremia or increased for hypernatremia. Although weight gain indicates excess fluid, water intake is not decreased if serum Na remains normal; instead, dietary Na is restricted.

Na and K intake is minimized except in patients with prior deficiencies or GI losses. An adequate diet should be provided, including daily protein intake of about 0.8 to 1 g/kg. If oral or enteral nutrition is impossible, parenteral nutrition is used, but in ARF, risks of fluid overload, hyperosmolality, and infection are increased by IV nutrition. Ca salts (carbonate, acetate) or synthetic non-Ca-containing phosphate binders before meals help maintain serum phosphate at < 5 mg/dL (< 1.78 mmol/L). To help maintain serum K at < 6 mmol/L in the absence of dialysis, a cation-exchange resin, Na polystyrene sulfonate, is given 15 to 60 g po or rectally 1 to 4 times/day as a suspension in water or in a syrup (eg, 70% sorbitol). An indwelling bladder catheter is rarely needed and should be used only when necessary because of an increased risk of UTI and urosepsis.

In many patients, a brisk and even dramatic diuresis after relief of obstruction is a physiologic response to the expansion of ECF during obstruction and does not compromise volume status. However, polyuria accompanied by the excretion of large amounts of Na, K, Mg, and other solutes may cause hypokalemia, hyponatremia, hypernatremia, hypomagnesemia, or marked contraction of ECF volume with peripheral vascular collapse. In this postoliguric phase, close attention to fluid and electrolyte balance is mandatory. Overzealous administration of salt and water after relief of obstruction can prolong diuresis. When postoliguric diuresis occurs, replacement of urine output with 0.45% saline at about 75% of urine output prevents volume depletion and the tendency for excessive free water loss while allowing the body to eliminate excessive volume if this is the cause of the polyuria.

Prevention

ARF can often be prevented by maintaining normal fluid balance, blood volume, and BP in patients with trauma, burns, or major hemorrhage and in those undergoing major surgery. Infusion of isotonic saline and blood may be helpful. Use of contrast agents should be minimized, particularly in at-risk groups (eg,

the elderly and those with preexisting renal insufficiency, volume depletion, diabetes, or heart failure). If contrast agents are necessary, risk can be lowered by minimizing volume of the IV contrast agent, using nonionic and low osmolal or iso-osmolal contrast agents, avoiding NSAIDs, and pretreating with normal saline at 1 mL/kg/h IV for 12 h before the test. Isotonic $NaHCO_3$ has been used successfully instead of normal saline in some patients. However, further study is needed to confirm this finding. *N*-acetylcysteine 600 mg po bid the day before and the day of IV contrast administration has been used to prevent contrast nephropathy, but reports of its efficacy are conflicting.

Before cytolytic therapy is initiated in patients with certain neoplastic diseases (eg, lymphoma, leukemia), treatment with allopurinol should be considered along with increasing urine flow by increasing oral or IV fluids to reduce urate crystalluria. Making the urine more alkaline (by giving oral or IV $NaHCO_3$ or acetazolamide) has been recommended by some but is controversial because it may also induce urinary Ca phosphate precipitation and crystalluria, which may cause ARF.

The renal vasculature is very sensitive to endothelin, a potent vasoconstrictor that reduces renal blood flow and GFR. Endothelin is implicated in progressive renal damage, and endothelin receptor antagonists have successfully slowed or even halted experimental renal disease. Antiendothelin antibodies and endothelin-receptor antagonists are being studied to protect the kidney against ischemic ARF.

Chronic Kidney Disease

(Chronic Renal Failure)

Chronic kidney disease (CKD) is long-standing, progressive deterioration of renal function. Symptoms develop slowly and include anorexia, nausea, vomiting, stomatitis, dysgeusia, nocturia, lassitude, fatigue, pruritus, decreased mental acuity, muscle twitches and cramps, water retention, undernutrition, GI ulceration and bleeding, peripheral neuropathies, and seizures. Diagnosis is based on laboratory testing of renal function, sometimes followed by renal biopsy. Treatment is primarily directed at the underlying condition but includes fluid and electrolyte management, erythropoietin for anemia, and often dialysis or transplantation.

Etiology

CKD may result from any cause of renal dysfunction of sufficient magnitude (see Table 239-4). The most common cause in the US is diabetic nephropathy (see p. 869), followed by hypertensive nephroangiosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome (see p. 64), in which hypertension and type 2 diabetes are present, is a large and growing cause of renal damage.

Pathophysiology

CKD can be roughly categorized as diminished renal reserve, renal insufficiency, or renal failure (end-stage renal disease). Initially, as renal tissue loses function, there are few abnormalities because the remaining tissue increases its performance (renal functional adaptation); a loss of 75% of renal tissue causes a fall in GFR to only 50% of normal.

Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis. Changes proceed predictably, but considerable overlap and individual variation exist. The ability to concentrate urine declines early and is followed by decreases in ability to excrete phosphate, acid, and K. When renal failure is advanced (GFR ≤ 10 mL/min/1.73 m^2), the ability to dilute urine is lost; thus urine osmolality is usually fixed close to that of plasma (300 to 320 mOsm/kg), and urinary volume does not respond readily to variations in water intake.

Plasma concentrations of creatinine and urea (which are highly dependent on glomerular filtration) begin a nonlinear rise as GFR diminishes. These changes are minimal early on. When the GFR falls below 10 mL/min/1.73 m^2 (normal = 100 mL/min/1.73 m^2), their levels increase rapidly and are usually

[Table 239-4. Major Causes of Chronic Kidney Disease]

associated with systemic manifestations (uremia). Urea and creatinine are not major contributors to the uremic symptoms; they are markers for many other substances (some not yet well defined) that cause the symptoms.

Despite a diminishing GFR, Na and water balance is well maintained by increased fractional excretion of Na and a normal response to thirst. Thus, the plasma Na concentration is typically normal, and hypervolemia is infrequent unless dietary intake of Na or water is very restricted or excessive. Heart failure can occur from Na and water overload, particularly in patients with decreased cardiac reserve.

For substances whose secretion is controlled mainly through distal nephron secretion (eg, K), adaptation usually maintains plasma levels at normal until renal failure is advanced. K-sparing diuretics, ACE inhibitors, β-blockers, NSAIDs, cyclosporine, tacrolimus, or angiotensin II receptor blockers may raise plasma K levels in patients with less advanced renal failure.

Abnormalities of Ca, phosphate, parathyroid hormone (PTH), vitamin D metabolism, and renal osteodystrophy can occur. Decreased renal production of calcitriol contributes to hypocalcemia. Decreased renal excretion of phosphate results in hyperphosphatemia. Secondary hyperparathyroidism is common and can develop in renal failure before abnormalities in Ca or phosphate concentrations occur. For this reason, monitoring PTH in patients with moderate CKD, even before hyperphosphatemia occurs, has been recommended.

Renal osteodystrophy (abnormal bone mineralization resulting from hyperparathyroidism, calcitriol deficiency, elevated serum phosphate, or low or normal serum Ca) usually takes the form of increased bone turnover due to hyperparathyroid bone disease (osteitis fibrosa) but can also involve decreased bone turnover due to adynamic bone disease (with increased parathyroid suppression) or osteomalacia. Calcitriol deficiency may cause osteopenia or osteomalacia.

Moderate acidosis (plasma HCO_3 content 15 to 20 mmol/L) and anemia are characteristic. The anemia of CKD is normochromicnormocytic, with an Hct of 20 to 30% (35 to 50% in patients with polycystic kidney disease). It is usually caused by deficient erythropoietin production due to a reduction of functional renal mass (see Ch. 105). Other causes include deficiencies of iron, folate, and vitamin B_{12}.

Symptoms and Signs

Patients with mildly diminished renal reserve are asymptomatic. Even patients with mild to moderate renal insufficiency may have no symptoms despite elevated BUN and creatinine. Nocturia is often noted, principally due to a failure to concentrate the urine. Lassitude, fatigue, anorexia, and decreased mental acuity often are the earliest manifestations of uremia.

With more severe renal insufficiency (eg, creatinine clearance < 10 mL/min for patients without diabetes and < 15 mL/min for those with diabetes), neuromuscular symptoms may be present, including coarse muscular twitches, peripheral sensory and motor neuropathies, muscle cramps, hyperreflexia, and seizures (usually the result of hypertensive or metabolic encephalopathy). Anorexia, nausea, vomiting, weight loss, stomatitis, and an unpleasant taste in the mouth are almost uniformly present. The skin may be yellow-brown. Occasionally, urea from sweat crystallizes on the skin (uremic frost). Pruritus may be especially uncomfortable. Undernutrition leading to generalized tissue wasting is a prominent feature of chronic uremia.

In advanced CKD, pericarditis and GI ulceration and bleeding are common. Hypertension is present in > 80% of patients with advanced CKD, is usually related to hypervolemia, and is occasionally the result of activation of the renin-angiotensin-aldosterone system. Heart failure caused by hypertension or coronary artery disease and renal retention of Na and water may lead to dependent edema.

Diagnosis

• Electrolytes, BUN, creatinine, phosphate, Ca, CBC, urinalysis (including urinary sediment examination)

• Ultrasonography

• Sometimes renal biopsy

CKD is usually first suspected when serum creatinine rises. The initial step is to determine whether the renal failure is acute, chronic, or acute superimposed on chronic (ie, an acute disease that further compromises renal function in a patient with CKD—see Table 239-5). The cause of renal failure is also determined. Sometimes determining the duration of renal failure helps determine the cause; sometimes it is easier to determine the cause than the duration, and determining the cause helps determine the duration.

Testing includes urinalysis with examination of the urinary sediment, electrolytes, urea nitrogen, and creatinine, phosphate, Ca, and CBC. Sometimes specific serologic tests are needed to determine the cause. Distinguishing acute from chronic renal failure is most helped by a history of an elevated creatinine

[**Table 239-5.** Distinguishing Acute Kidney Failure from Chronic Kidney Disease]

level or abnormal urinalysis. Urinalysis findings depend on the nature of the underlying disorder, but broad (> 3 WBC diameters wide) or especially waxy (highly refractile) casts often are prominent in advanced renal failure of any cause.

An ultrasound examination of the kidneys is usually helpful in evaluating for obstructive uropathy and in distinguishing acute from chronic renal failure based on kidney size. Except in certain conditions (see Table 239-4), patients with chronic renal failure have small shrunken kidneys (usually < 10 cm in length) with thinned, hyperechoic cortex. Obtaining a precise diagnosis becomes increasingly difficult as renal function reaches values close to those of end-stage renal disease. The definitive diagnostic tool is renal biopsy, but it is not recommended when ultrasonography indicates small, fibrotic kidneys.

Classification: Staging CKD is a way of quantifying its severity. CKD has been classified into 5 stages.

• Stage 1: Normal GFR (≥ 90 mL/min/1.73 m^2) plus either persistent albuminuria or known structural or hereditary renal disease

• Stage 2: GFR 60 to 89 mL/min/1.73 m^2

• Stage 3: GFR 30 to 59 mL/min/1.73 m^2

• Stage 4: GFR 15 to 29 mL/min/1.73 m^2

• Stage 5: GFR < 15 mL/min/1.73 m^2

GFR (in mL/min/1.73 m^2) in CKD can be estimated by: $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$. The result is multiplied by 0.742 if the patient is female and by 1.21 if African American. For female African Americans, the result is multiplied by 0.742 × 1.21 (0.898).

Prognosis

Progression of CKD is predicted in most cases by the degree of proteinuria. Patients with nephrotic-range proteinuria (> 3 g/24 h or urine protein/creatinine > 3) usually have a poorer prognosis and progress to renal failure more rapidly. Progression may occur even if the underlying disorder is not active. In patients with urine protein < 1.5 g/24 h, progression usually occurs more slowly if at all. Hypertension is associated with more rapid progression as well.

Treatment

• Control of underlying disorders

• Possible restriction of dietary protein, phosphate, and K

• Vitamin D supplements

• Treatment of anemia and heart failure

• Doses of all drugs adjusted as needed

• Dialysis for severely decreased GFR, uremic symptoms, or sometimes hyperkalemia or heart failure

Underlying disorders and contributory factors must be controlled. In particular, controlling hyperglycemia in patients with diabetic nephropathy and controlling hypertension in all patients substantially slows deterioration of GFR. Target BP should be about 110 to 130/< 80 mm Hg. ACE inhibitors and angiotensin II receptor blockers decrease the rate of decline in GFR in patients with most causes of CKD, particularly those with proteinuria.

Activity need not be restricted, although fatigue and lassitude usually limit a patient's capacity for exercise. Pruritus may respond to phosphate binders if serum phosphate is elevated. If patients do not respond, ultraviolet phototherapy may help.

Nutrition: Severe protein restriction in renal disease is controversial. However, moderate restriction (0.8 g/kg/day) is safe and easy for most patients to tolerate. Some experts recommend 0.6 g/kg/day for patients with diabetes and, for patients without diabetes, > 0.8 g/kg/day if GFR is 25 to 55 mL/min/1.73 m^2 or 0.6 g/kg/day if GFR is 13 to 24 mL/min/1.73 m^2. Many uremic symptoms markedly lessen when protein catabolism and urea generation are reduced. Sufficient carbohydrate and fat are given to meet energy requirements and prevent ketosis. Patients for whom < 0.8 g/kg/day has been prescribed should be closely followed by a dietician.

Because dietary restrictions may reduce necessary vitamin intake, patients should take a multivitamin containing water-soluble vitamins. Administration of vitamin A and E is unnecessary. Vitamin D in the form of 1,25-dihydroxyvitamin D (calcitriol) or its analogs should be given as indicated by PTH concentrations. Dose is determined by stage of CKD, PTH concentration, and phosphate concentrations (see Table 239-6). Target levels for Ca are 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L); for the Ca-phosphate product, < 55 mg^2/dL^2.

A typical starting dose is calcitriol (or a calcitriol analog) 0.25 µg po once/day or 1 to 4 µg 2 times/wk. PTH levels are not corrected to normal because doing so risks precipitating adynamic bone disease.

Dietary modification may be helpful for hypertriglyceridemia. In patients with hypercholesterolemia, a statin is effective. Fibric acid derivatives (clofibrate, gemfibrozil) may increase risk of rhabdomyolysis in patients with CKD, especially if taken with statin drugs, whereas ezetimibe (which reduces cholesterol absorption) appears relatively safe. Correction of hypercholesterolemia may slow progression of the underlying renal disease and reduce coronary risk.

Fluid and electrolytes: Water intake is restricted only when serum Na concentration is < 135 mmol/L.

Na restriction of 2 g/day benefits patients, especially those with edema, heart failure, or hypertension.

K intake is closely related to meat, vegetable, and fruit ingestion and usually does not require adjustment. However, foods (especially salt substitutes) rich in K should generally be avoided. Hyperkalemia is infrequent (unless there is hyporeninemic hypoaldosteronism or K-sparing diuretic therapy) until end-stage renal failure, when intake may need to be restricted to ≤ 50 mmol/day. Mild hyperkalemia (< 6 mmol/L) can be treated by reducing K intake and correcting metabolic acidosis. More severe hyperkalemia (> 6 mmol/L) warrants urgent treatment (see pp.

836 and 2440).

Phosphate restriction to < 1 g/day is often sufficient to maintain phosphate level in the target range during the early phase of stages 3 and 4 CKD. However, in the later phases, phosphate binders, such as Ca salts (acetate or carbonate but avoid citrate) or non-Ca-containing phosphate binders (sevelamer) are often necessary. No more than 1500 mg/day of elemental Ca should be given as binders (2000 mg/day of total Ca; binders plus dietary Ca).

Mild **acidosis** (pH 7.30 to 7.35) requires no therapy. However, most patients with chronic metabolic acidosis who have a pH < 7.3 have a plasma HCO_3 content < 15 mmol/L and symptoms of anorexia, lassitude, dyspnea, and exaggerated protein catabolism and renal osteodystrophy. $NaHCO_3$ 1 to 2 g po bid is given and amount is increased gradually until HCO_3 concentration is about 20 mEq/L or until evidence of Na overloading prevents further therapy.

Anemia and coagulation disorders: Anemia is treated to keep the Hb between 11 and 12 g/dL. Anemia slowly responds to recombinant human erythropoietin (eg, epoetin alfa 50 to 150 units/kg sc 1 to 3 times/wk). Because of increased iron utilization with stimulated erythropoiesis, iron stores must be replaced, usually with parenteral iron. Iron concentrations, iron-binding capacity, and ferritin concentrations should be followed closely. Transfusion should not be undertaken unless anemia is severe (Hb < 8 g/dL) or causes symptoms.

The bleeding tendency in CKD rarely needs treatment. Cryoprecipitate, RBC transfusions, desmopressin 0.3 to 0.4 µg/kg (20 µg maximum) in 20 mL of isotonic saline IV over 20 to 30 min, or conjugated estrogens 2.5 to 5 mg po once/day help when needed. The effects of these treatments last 12 to 48 h, except for conjugated estrogens, which may last for several days.

Heart failure: Symptomatic heart failure is treated with Na restriction and diuretics

[**Table 239-6.** Target Levels for PTH and Phosphate in Chronic Kidney Disease]

(see p. 2128). If left ventricular function is depressed, ACE inhibitors and β-blockers (carvedilol or metoprolol) should be used. Digoxin may be added, but the dosage must be reduced. Diuretics such as furosemide usually are effective even when renal function is markedly reduced, although large doses may be needed. Moderate or severe hypertension should be treated to avoid its deleterious effects on cardiac and renal function. Patients who do not respond to moderate reduction in Na intake (4 g/day) need further dietary Na restriction (2 g/day) and diuretic therapy (furosemide 80 to 240 mg po bid). Hydrochlorothiazide 50 mg po bid or metolazone 5 to 10 mg po once/day may be added to high-dose furosemide therapy if hypertension or edema is not controlled. Even in renal failure, the combination of a thiazide with a loop diuretic is quite potent and must be used with caution to avoid overdiuresis. Occasionally, dialysis may be required to control heart failure. If reduction of the ECF volume does not control BP, conventional antihypertensives are added. Azotemia may increase with such treatment but is acceptable short-term, even if temporary dialysis is required.

Drugs: Renal excretion of drugs is often impaired in patients with renal failure. Common drugs that require revised dosing include penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, and digoxin. Hemodialysis reduces the serum concentrations of some drugs, which should be supplemented after hemodialysis. It is strongly recommended that physicians consult a reference on drug dosing in renal failure before prescribing drugs to these very vulnerable patients.

Certain drugs should be avoided entirely in patients undergoing dialysis. They include nitrofurantoin, metformin, and phenazopyridine.

Dialysis: Dialysis is initiated when GFR reaches ≤ 10 mL/min in a patient without diabetes or ≤ 15 mL/min in a patient with diabetes. Patients with uremic symptoms (eg, anorexia, vomiting, weight loss, pericarditis, pleuritis) or fluid overload who have no other conditions that would explain these symptoms should be started on dialysis even if GFR has not reached these levels. Other indications for dialysis in chronic kidney disease include hyperkalemia that causes ECG changes or that is persistent (K > 6

mmol/L) despite dietary restriction, heart failure poorly controlled with drugs, and metabolic acidosis that is difficult to control. (For dialysis preparation, see p. 2447.)

Transplantation: If a living kidney donor is available, better long-term outcomes occur when a patient receives the transplanted kidney early, even before beginning dialysis. Patients who are transplant candidates but have no living donor should receive a cadaveric renal transplant as early after initiating dialysis as possible (see p. 1133).

Chapter 240. Renal Replacement Therapy

Introduction

Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include intermittent hemodialysis, continuous hemofiltration and hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes.

RRT does not correct the endocrine abnormalities (decreased erythropoietin and 1,25-dihydroxyvitamin D_3 production) of renal failure. In dialysis, serum solute (eg, Na, Cl, K, HCO_3, Ca, Mg, phosphate, urea, creatinine, uric acid) diffuses passively between fluid compartments down a concentration gradient (diffusive transport). In filtration, serum water passes between compartments down a hydrostatic pressure gradient, dragging solute with it (convective transport). The two processes are often used in combination (hemodiafiltration). Hemoperfusion is a rarely used technique that removes toxins by flowing blood over a bed of adsorbent material (usually a resin compound or charcoal).

Dialysis and filtration can be done intermittently or continuously. Continuous therapy is used exclusively for acute renal failure; benefits over intermittent therapy are improved tolerability as a result of slower removal of solute and water. All forms of RRT except peritoneal dialysis require vascular access; continuous techniques require a direct arteriovenous or venovenous circuit.

The choice of technique depends on multiple factors, including the primary need (eg, solute or water removal or both), underlying indication (eg, acute or chronic kidney failure, poisoning), vascular access, hemodynamic stability, availability, local expertise, and patient preference.
Table 240-1 lists indications and contraindications for the common forms of RRT.

Care of patients requiring long-term RRT ideally involves a nephrologist, a psychiatrist, a social worker, a renal dietitian, dialysis nurses, and the transplant surgical team. Patient assessment should begin when end-stage renal failure is anticipated but before RRT is needed, so that care can be coordinated and patients can be educated about their options, evaluated for resources and needs, and have vascular access created. Psychosocial evaluation is important because RRT makes patients socially and emotionally vulnerable. It interrupts routine work, school, and leisure activities; creates anger, frustration, tension, and guilt surrounding dependency; and alters body image because of reduced physical energy, loss or change in sexual function, changed appearance due to access surgery, dialysis catheter placement, needle marks, bone disease, or other physical deterioration. Some patients express these feelings by nonadherence or by being uncooperative with the treatment team. Personality traits that improve prognosis for successful long-term adjustment include adaptability, independence, self-control, tolerance for frustration, and optimism. Emotional stability, family encouragement, consistent treatment team support, and patient and family participation in decision making are also important. Programs that encourage patient independence and maximal resumption of former life interests are more successful in decreasing psychosocial problems.

Hemodialysis

(Intermittent Hemodialysis)

In hemodialysis, a patient's blood is pumped into a dialyzer containing 2 fluid compartments configured as bundles of hollow fiber capillary tubes or as parallel, sandwiched sheets of semipermeable membranes. In either configuration, blood in the first compartment is pumped along one side of a semi-permeable membrane while a crystalloid solution (dialysate) is pumped along the other side, in a separate compartment, in the opposite direction. Concentration gradients of solute between blood and dialysate lead to desired changes in the patient's serum solutes, such as a reduction in urea nitrogen and creatinine; an increase in HCO_3; and equilibration of Na, Cl, K, and Mg. The dialysate compartment is under negative pressure relative to the blood compartment to prevent filtration of dialysate into the bloodstream and to remove the excess fluid from the patient. The dialyzed blood is then returned to the patient.

The patient is usually systemically anticoagulated during hemodialysis to prevent blood from clotting in the dialysis machine. However hemodialysis treatment may also be done with regional anticoagulation of the

[**Table 240-1.** Indications and Contraindications to Common Renal Replacement Therapies]

dialysis circuit (using heparin or trisodium citrate) or with saline flush, in which 50 to 100 mL of saline every 15 to 30 min clears the dialysis circuit of any blood clots.

The immediate objectives of hemodialysis are to correct electrolyte and fluid imbalances and remove toxins. Longer-term objectives in patients with renal failure are to

• Optimize the patient's functional status, comfort, and BP

• Prevent uremia and its complications

• Improve survival

The optimal "dose" of hemodialysis is uncertain, but most patients do well with 3 to 5 h of hemodialysis 3 times/wk. One way to assess the adequacy of each session is by measuring BUN before and after each session. A ≥ 65% decrease of BUN from predialysis level ([predialysis BUN - postdialysis BUN]/predialysis BUN × 100% is ≥ 65%) indicates an adequate session. Specialists may use other, more calculation-intensive formulas, such as KT/V ≥ 1.2 (where K is the urea clearance of the dialyzer in mL/min, T is dialysis time in minutes, and V is volume of distribution of urea [total body water] in mL). Hemodialysis dose can be increased by increasing time on dialysis, blood flow, membrane surface area, and membrane porosity, but benefits are unproven. Nightly hemodialysis sessions (6 to 8 h, 5 to 6 days/wk) and short (1.5- to 2.5-h) daily sessions are being studied as ways to increase effectiveness and decrease complications.

Vascular access: Hemodialysis is usually done through a surgically created arteriovenous fistula. However, dialysis can be done through a central vein catheter if an arteriovenous fistula has not yet been created or is not ready for use or if creation of an arteriovenous fistula is impossible. The primary disadvantages of central vein catheters are a relatively narrow caliber that does not allow for blood flow high enough to achieve optimal clearance and a high risk of catheter site infection and thrombosis. Central venous catheterization for hemodialysis is best done by using the right internal jugular vein. Most internal jugular vein catheters remain useful for 2 to 6 wk if strict aseptic skin care is practiced and if the catheter is used only for hemodialysis. Also, catheters with a subcutaneous tunnel and fabric cuff have a longer life span (50% functional at 1 yr) and may be useful for patients in whom creation of an arteriovenous fistula is impossible.

Surgically created arteriovenous fistulas are better than central venous catheters because they are more durable and less likely to become infected. But they are also prone to complications (thrombosis, infection, aneurysm or pseudoaneurysm). A newly created fistula may take 3 to 6 mo to mature and be useable, so in patients with chronic renal failure, the fistula should be created early, when GFR is between 25 and 30 mL/min. The surgical procedure anastomoses the radial, brachial, or femoral artery to an adjacent vein in an end-of-the-vein to the side-of-the-artery fashion. When the adjacent vein is not suitable for access creation, a piece of prosthetic graft is used. For patients who have poor veins, an autogenous saphenous vein graft is also an option.

Vascular access complications: Complications such as infection, thrombosis, and pseudoaneurysm or aneurysm, significantly limit the quality of hemodialysis that can be delivered, increase long-term morbidity and mortality, and are common enough that patients and practitioners should be vigilant for suggestive changes. These changes include pain, erythema, breaks in the skin overlying the access, absence of bruit and pulse in the access, hematoma around the access, and prolonged bleeding from the dialysis cannula puncture site. Infection is treated with antibiotics, surgery, or both.

The fistula may be monitored for signs of impending failure by serial Doppler dilution blood flow

measurements, thermal or urea dilution techniques, or by measurement of the static venous chamber pressures. One of these tests is usually recommended at least monthly. Treatment of thrombosis, pseudoaneurysm, or aneurysm may involve angioplasty, stenting, and surgery.

Dialysis complications: Complications are listed in Table 240-2.

Hypotension is most common and has multiple causes, including too-rapid water removal, osmotic fluid shifts across cell membranes, acetate in dialysate, heat-related vasodilation, and underlying conditions (eg, autonomic neuropathy, myocardial ischemia, arrhythmias).

Many patients also experience cramps, pruritus, nausea and vomiting, headache, and chest and back pain. In most cases, these complications occur for unknown reasons, but some may be part of a first-use syndrome (when the patient's blood is exposed to cuprophane or cellulose membranes in the dialyzer) or dialysis disequilibrium syndrome, a syndrome thought to be caused by cerebral edema. More severe cases of dialysis dys-equilibrium manifest as disorientation, restlessness, blurred vision, confusion, seizures, and even death.

Dialysis amyloidosis affects patients who have been on hemodialysis for years and manifests as carpal tunnel syndrome, bone cysts, arthritis, and cervical spondyloarthropathy.

Prognosis: Overall adjusted annual mortality in hemodialysis-dependent patients tends to be about 20%. The 5-yr survival rate is lower for patients with diabetes than for patients with glomerulonephritis. Death is generally mostly attributable to cardiovascular disease, followed by infection and withdrawal from hemodialysis. Blacks have usually had a higher survival rate in all age groups. Nonhemodialysis contributors to mortality include comorbidities (eg, hyperparathyroidism, diabetes), age, undernutrition, and late referral for dialysis.

Continuous Hemofiltration and Hemodialysis

Continuous hemofiltration and hemodialysis procedures filter and dialyze blood without interruption. The principal advantage is the ability to remove large volumes of fluid while

[**Table 240-2.** Complications of Renal Replacement Therapy]

avoiding the hypotensive episodes caused by intermittent hemodialysis and its intermittent removal of large volumes of fluid. These procedures are therefore indicated for managing patients with acute renal failure who are hemo-dynamically unstable, who must receive large volumes of fluid (eg, patients with multiple organ system failure or shock who require hyperalimentation or vasopressor drips), or both.

In continuous hemofiltration, water and solutes up to 20,000 daltons in molecular weight filter from the blood by convection through a permeable membrane; the filtrate is discarded, and the patient must receive infusions of physiologically balanced water and electrolytes. A dialysis circuit can be added to the filter to improve solute clearance. Procedures may be arteriovenous or venovenous. In arteriovenous procedures, the femoral artery is cannulated, and arterial pressure pushes blood through the filter into the femoral vein. Filtration rates are typically low, especially in hypotensive patients. In continuous venovenous procedures, a pump is required to push blood from one large vein (femoral, subclavian, or internal jugular) through the dialysis circuit and back into the venous circulation. Using a double-lumen catheter, blood is drawn from and returned to the same vein.

The arteriovenous route has the advantage of a simple system without the requirement of a pump but may give unreliable blood flows in hypotensive patients. Advantages of the venovenous route include better control of BP and filtration rate with smoother removal of fluid. Also, the venovenous route requires cannulation of only one vessel. Neither procedure is proven more effective than the other. All require systemic anticoagulation.

Peritoneal Dialysis

Peritoneal dialysis uses the peritoneum as a natural permeable membrane through which water and solutes can equilibrate. Peritoneal dialysis is less physiologically stressful than hemodialysis, does not require vascular access, can be done at home, and allows patients much greater flexibility. However, it requires much more patient involvement. Of the total estimated resting splanchnic blood flow of 1200 mL/min, only about 70 mL/min comes into contact with the peritoneum, so solute equilibration occurs much more slowly than in hemodialysis. But because solute and water clearance is a function of contact time and peritoneal dialysis is done nearly continuously, efficacy in terms of solute removal is equivalent to that obtained with hemodialysis.

In general, dialysate is instilled through a catheter into the peritoneal space, is left to dwell, and then drained. In the double-bag technique, the patient drains the fluid instilled in the abdomen in one bag and then infuses fluid from the other bag into the peritoneal cavity.

Continuous ambulatory peritoneal dialysis (CAPD) is most commonly used because of ease of performance and lack of need for a machine to do the exchanges. A typical adult infuses 2 to 3 L (children, 30 to 40 mL/kg) of dialysate 4 to 5 times/day; dialysate is allowed to remain for 4 h during the day and 8 to 12 h at night. The solution is manually drained. Flushing the infusion set before filling reduces peritonitis rates.

Continuous cyclic peritoneal dialysis (CCPD) uses a long (12 to 15 h) daytime dwell and 3 to 6 nighttime exchanges done with an automated cycler. Patients have more freedom during the day, but cumbersome equipment inhibits nighttime mobility. Some patients require a combination of CAPD and CCPD to achieve adequate clearances.

Intermittent peritoneal dialysis (IPD) may be done using manual or automated techniques or both. Manual IPD is simplest, achieves the highest solute clearance, and is useful chiefly in the treatment of acute renal failure. In adults, 2 to 3 L (in children, 30 to 40 mL/kg) of dialysate, warmed to 37° C, is infused over 10 to 15 min, allowed to dwell in the peritoneal cavity for 30 to 40 min, and drained in about 10 to 15 min. Multiple exchanges may be needed over 12 to 48 h. Automated cycler IPD uses an automated system that cycles the infusion and removal of dialysate. The cycler is generally set up at bedtime, and treatment occurs while the patient sleeps.

Access: Peritoneal dialysis requires intraperitoneal access, usually via a soft silicone rubber or porous polyurethane catheter. The catheter may be implanted in the operating room under direct visualization or at the bedside by blind insertion of a trocar or under visualization through a peritoneoscope. Most catheters incorporate a polyester fabric cuff that allows tissue ingrowth from the skin or preperitoneal fascia, ideally resulting in a watertight, bacteria-impervious seal and preventing introduction of organisms along the catheter tract. Allowing 10 to 14 days between catheter implantation and use improves healing and reduces the frequency of early pericatheter leakage of dialysate. Double-cuff catheters are better than single-cuff catheters. Also, a caudally directed exit site (the opening of the tunnel through which the catheter enters the peritoneal cavity) lowers the incidence of exit site infections (eg, by collecting less water while showering).

Once access is established, the patient undergoes a peritoneal equilibration test, in which dialysate drained after a 4-h dwell time is analyzed and compared with serum to determine solute clearance rates. This procedure helps determine the patient's peritoneal transport characteristics, the dose of dialysis required, and the most appropriate technique. In general, adequacy is defined as a weekly $KT/V \geq 1.7$ (where K is the urea clearance in mL/min, T is dialysis time in minutes, and V is volume of distribution of urea [total body water] in mL).

Complications: (See also Table 240-2). The most important and common are peritonitis and catheter exit site infection. Symptoms and signs of peritonitis include abdominal pain, cloudy peritoneal fluid, fever, nausea, and tenderness to palpation. Diagnosis is made by clinical criteria and testing. A sample of peritoneal fluid is obtained for Gram stain, culture, and WBC count with differential. Gram stain is often unrevealing, but cultures are positive in > 90%. About 90% also have > 100 WBCs/μL, usually neutrophils (lymphocytes with fungal peritonitis). Negative cultures and WBC counts < 100/μL do not exclude peritonitis, so treatment is indicated if peritonitis is suspected based on clinical or laboratory criteria and should begin immediately, before culture results are available. Peritoneal fluid studies may be falsely

negative due to prior antibiotic use, infection limited to the catheter exit site or tunnel, or sampling of too little fluid.

Empiric treatment should be adapted to microbial resistance patterns of a given facility, but typical recommendations are for initial treatment with drugs active against gram-positive organisms, eg, either vancomycin or a 1st-generation cephalosporin, plus drugs active against gram-negative organisms, such as a 3rd-generation cephalosporin (eg, ceftazidime) or an aminoglycoside (eg, gentamicin). Drugs are adjusted based on the result of peritoneal dialysis fluid culture. Antibiotic therapy is usually given IV or intraperitoneally (IP) for peritonitis and orally for exit site infections. Patients with peritonitis are admitted to the hospital if IV treatment is necessary or if hemodynamic instability or other significant complications arise.

Catheter tunnel exit site infection manifests as tenderness over the tunnel or at the exit site along with crusting, erythema, or drainage. Diagnosis is clinical. Treatment of infection without drainage is topical antiseptics (eg, povidone iodine, chlorhexidine); if ineffective, a 1st-generation cephalosporin or a penicillinase-resistant penicillin is used empirically, with culture results guiding subsequent therapy.

Prognosis: Most cases of peritonitis respond to prompt antibiotic therapy, but those caused by staphylococci or fungi also require dialysis catheter removal. Overall, 5-yr survival rate in peritoneal dialysis patients is similar to that in hemodialysis patients (about 36%).

Medical Aspects of Long-Term Renal Replacement Therapy

All patients undergoing long-term renal replacement therapy (RRT) develop accompanying metabolic and other disorders. These disorders require appropriate attention and adjunctive treatment. Approach varies by patient but typically includes nutritional modifications and management of multiple metabolic abnormalities (see also p. 2445).

Diet: Diet should be tightly controlled. Generally, hemodialysis patients tend to be anorexic and should be encouraged to eat a daily diet of 35 kcal/kg ideal body weight (in children, 40 to 70 kcal/kg/day depending on age and activity). Daily Na intake should be limited to 2 g (88 mEq), K to 60 mEq, and P to 800 to 1000 mg. Fluid intake is limited to 1000 to 1500 mL/day and monitored by weight gain between dialysis treatments. Patients undergoing peritoneal dialysis need a protein intake of 1.25 to 1.5 g/kg/day (compared with 1.0 to 1.2 g/kg/day in hemodialysis patients) to replace peritoneal losses (10 to 20 g/day). Survival is best among patients (both hemodialysis and peritoneal dialysis) who maintain a serum albumin > 3.5 g/dL; serum albumin is the best predictor of survival in these patients.

Anemia of renal failure: The anemia that occurs in renal failure should be treated with recombinant human erythropoietin and iron supplementation (see p. 2445). Because the absorption of oral iron is limited, many patients require IV iron during hemodialysis (Na ferric gluconate and iron sucrose are preferred to iron dextran, which has a higher incidence of anaphylaxis). Iron stores are assessed using serum iron, total iron-binding capacity, and serum ferritin, typically before the start of erythropoietin therapy and thereafter every other month. Iron deficiency is the most common reason for erythropoietin resistance. However, some dialysis patients who have received multiple blood transfusions have iron overload (see p. 1032) and should not be given iron supplements.

Coronary artery disease: Risk factors must be managed aggressively because many patients who require RRT are hypertensive, dyslipidemic, or diabetic; smoke cigarettes; and ultimately die of cardiovascular disease. Continuous peritoneal dialysis is more effective than hemodialysis in removing fluid; as a result, these patients require fewer antihypertensive drugs. Hypertension can also be controlled in about 80% of hemodialysis patients by filtration alone. Antihypertensives are required in the remaining 20%. Patients given ACE inhibitors or angiotensin II receptor blockers may need closer monitoring of serum K^+ to prevent hyperkalemia. For approaches to dyslipidemia, see p. 896; for diabetes management, see p. 871; and for smoking cessation, see p. 3432.

Hyperphosphatemia: Hyperphosphatemia, a consequence of phosphate retention from low GFR, increases risk for soft-tissue calcification, especially in coronary arteries and heart valves, when Ca × P > 70. It also stimulates development of secondary hyperparathyroidism. Initial treatment is Ca-based

antacids (eg, Ca carbonate 1.25 g po tid, Ca acetate 667 to 2001 mg po tid with meals), which function as phosphate binders and reduce P levels. Constipation and abdominal bloating are complications of chronic use. Patients should be monitored for hypercalcemia. Sevelamer hydrochloride 800 to 3200 mg or lanthanum carbonate 250 to 1000 mg with each meal is an option for patients who develop hypercalcemia while taking Ca-containing phosphate binders. Some patients (eg, those hospitalized with acute renal failure and very high serum phosphate concentrations) require addition of aluminum-based phosphate binders, but these should be used short-term only (eg, 1 to 2 wk as needed) to prevent aluminum toxicity.

Hypocalcemia and secondary hyperparathyroidism: These complications often coexist as a result of impaired renal production of vitamin D. Treatment of hypocalcemia is with calcitriol either orally (0.25 to 1.0 µg po once/day) or IV (1 to 3 µg in adults and 0.01 to 0.05 µg/kg in children per dialysis treatment). Treatment can increase serum phosphate level and should be withheld until the level is normalized to avoid soft-tissue calcification. Doses are titrated to suppress parathyroid hormone (PTH) levels, usually to 150 to 300 pg/mL (PTH reflects bone turnover better than serum Ca). Oversuppression decreases bone turnover and leads to adynamic bone disease, which carries a high risk of fracture. The vitamin D analogs doxercalciferol and paricalcitol have less effect on Ca and P absorption from the gut but suppress PTH equally well. Early hints that these drugs may reduce mortality compared with calcitriol require confirmation. Cinacalcet, a calcimimetic drug, increases sensitivity of parathyroid Ca-sensing receptors to Ca and may also be indicated for hyperparathyroidism, but its role in routine practice has yet to be defined. Its ability to decrease PTH levels by as much as 75% may decrease the need for parathyroidectomy in these patients.

Aluminum toxicity: Toxicity is a risk in hemodialysis patients who are exposed to aluminum-based phosphate binders. Manifestations are osteomalacia, microcytic anemia (iron-resistant), and probably dialysis dementia (a constellation of memory loss, dyspraxia, hallucinations, facial grimaces, myoclonus, seizures, and a characteristic EEG). Diagnosis is by measurement of plasma aluminum before and 2 days after IV infusion of defer-oxamine 5 mg/kg. Deferoxamine chelates aluminum, releasing it from tissues and increasing the blood level among patients with aluminum toxicity. A rise in aluminum level of ≥ 50 µg/L suggests toxicity. Aluminum-related osteomalacia can also be diagnosed by needle biopsy of bone (requires special stains for aluminum). Treatment is avoidance of aluminum-based binders plus IV or intraperitoneal deferoxamine.

Bone disease: Renal osteodystrophy is abnormal bone mineralization. It has multiple causes, including vitamin D deficiency, elevated serum phosphate, secondary hyperparathyroidism, chronic metabolic acidosis, and aluminum toxicity; treatment is that of the cause.

Vitamin deficiencies: Vitamin deficiencies result from dialysis-related loss of water-soluble vitamins (eg, B, C, folate) and can be replenished with daily multivitamin supplements.

Calciphylaxis: Calciphylaxis is a rare disorder of systemic arterial calcification causing ischemia and necrosis in localized areas of the fat and skin of the trunk, buttocks, and lower extremities. Cause is unknown, though hyperparathyroidism, vitamin D supplementation, and elevated Ca and P levels are thought to contribute. It manifests as painful, violaceous, purpuric plaques and nodules that ulcerate, form eschars, and become infected. It is often fatal. Treatment is usually supportive. Several cases have been reported in which Na thiosul-fate given IV at the end of dialysis 3 times/wk along with aggressive efforts to reduce the serum Ca × phosphate product has resulted in considerable improvement.

Constipation: Constipation is a minor but troubling aspect of long-term RRT and, because of resulting bowel distention, may interfere with catheter drainage in peritoneal dialysis. Many patients require osmotic (eg, sorbitol) or bulk (eg, psyllium) laxatives. Laxatives containing Mg or phosphate should be avoided.

Chapter 241. Penile and Scrotal Disorders

Introduction

Abnormalities of the external male genitals are psychologically disturbing and sometimes serious (see p. 2985; for testicular and scrotal anomalies, see p. 2986).

Balanitis, Posthitis, and Balanoposthitis

Balanitis is inflammation of the glans penis, posthitis is inflammation of the prepuce, and balanoposthitis is inflammation of both.

Inflammation of the head of the penis has both infectious and noninfectious causes (see Table 241-1). Often, no cause can be found. Balanoposthitis often occurs in patients with a tight prepuce (phimosis), which interferes with adequate hygiene. The subpreputial secretions may become infected with anaerobic bacteria, resulting in inflammation. Diabetes mellitus predisposes to balanoposthitis. Balanitis usually leads to posthitis except in circumcised patients. Chronic balanoposthitis increases the risk of balanitis xerotica obliterans, phimosis, paraphimosis, and cancer.

Symptoms and Signs

Soreness, irritation, and a subpreputial discharge often occur 2 or 3 days after sexual intercourse. Phimosis, superficial ulcerations, and inguinal adenopathy may follow.

Diagnosis

Patients should be tested for the causes listed, especially candidiasis. Blood should be tested for glucose. The skin should be examined for lesions that suggest a dermatosis capable of genital involvement. History should include investigation of latex condom use.

Treatment

Hygiene measures should be instituted and specific causes treated. Subpreputial irrigation to remove secretions and detritus may be necessary. If phimosis persists after inflammation has resolved, circumcision should be considered.

Cutaneous Penile Lesions

Common skin disorders and infections can cause cutaneous penile lesions (see Table 241-2).

Balanitis xerotica obliterans: This lesion, another name for lichen sclerosus et atrophicus in men, is an indurated, blanched area near the tip of the glans surrounding and often constricting the meatus. It results from chronic inflammation and may lead to phimosis, paraphimosis, or urethral stricture. Topical drugs, including corticosteroids, tacrolimus, antibiotics, and anti-inflammatory drugs, may be used, but their efficacy is limited. Surgery is required in severe cases.

Carcinoma in situ: This lesion can include erythroplasia of Queyrat and Bowen's disease of the penis; both are well-circumscribed areas of reddish, velvety pigmentation in the genital area, usually on the glans or at the corona, primarily in uncircumcised men. Paget's disease of the nipple (not to be confused with Paget's disease of bone) is a rare intraepithelial adeno-carcinoma that can occur in extramammary locations, including the penis. These conditions (and Bowenoid papulosis, which involves smaller, often multiple papules on the shaft of the penis) are considered intraepithelial neoplasia or carcinoma in situ and should be biopsied. Treatment consists of 5% fluorouracil

[**Table 241-1.** Causes of Penile Inflammation]

[**Table 241-2.** Causes of Cutaneous Penile Lesions]

cream, local excision, or laser therapy. Close follow-up is indicated.

Penile lichen planus: This lesion occurs as small papules or macules, sometimes annular, on the glans or shaft and may be mistaken for pemphigoid or erythema multiforme. Pruritus is common. A more severe form of erosive lichen planus occurs on both oral and genital mucosa and is known as penogingival syndrome in men and vulvovaginal gingival syndrome in women. Ulcers may develop and cause pain. Lichen planus usually resolves spontaneously. If asymptomatic, it may not require treatment. Topical corticosteroids may help relieve symptoms.

Pearly penile papules: These papules are small, harmless angiofibromas that appear on the corona of the penis as dome-shaped or hairlike projections and tend to be skin-colored. They may also appear on the distal shaft. They are common, occurring in up to 10% of men. They are not associated with human papillomavirus, although they may be mistaken for genital warts. Treatment is not required.

Contact dermatitis of the penis: Contact dermatitis (see p. 666) of the penis has become more common with the widespread use of latex condoms. Dermatitis appears as red, pruritic lesions, sometimes with weeping or fissures. Treatment is with topical corticosteroids and use of nonlatex condoms (but not natural condoms, which do not provide adequate protection against HIV). Mild OTC corticosteroids can be tried first, with use of middle or high potency prescription preparations as needed.

Epididymitis

Epididymitis is inflammation of the epididymis, occasionally accompanied by inflammation of the testis (epididymo-orchitis). Scrotal pain and swelling usually occur unilaterally. Diagnosis is based on physical examination. Treatment is with antibiotics, analgesics, and scrotal support.

Etiology

Bacterial: Most epididymitis (and epididymoorchitis) is caused by bacteria. When inflammation involves the vas deferens, vasitis ensues. When all spermatic cord structures also are involved, the diagnosis is funiculitis. Rarely, epididymal abscess, scrotal extra-epididymal abscess, pyocele (accumulation of pus within a hydrocele), or testicular infarction occurs.

In men < 35 yr, most cases are due to a sexually transmitted pathogen, especially *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Infection may begin as urethritis. In men > 35 yr, most cases are due to gram-negative coliform bacilli and typically occur in patients with urologic abnormalities, indwelling catheters, or recent urologic procedures. Tuberculous epididymitis and syphilitic gummas are rare in the US except in immunocompromised (eg, HIV-infected) patients.

Nonbacterial: Viral causes (eg, cytomegalovirus infection) and mycotic causes (eg, actinomycosis, blastomycosis) are rare in the US except in immunocompromised (eg, HIV-infected) patients. Epididymitis and epididymo-orchitis of noninfectious etiology may be due to chemical irritation secondary to a retrograde flow of urine into the epididymis, which may occur with Valsalva maneuver (eg, with heavy lifting) or after local trauma.

Symptoms and Signs

Scrotal pain occurs in both bacterial and nonbacterial epididymitis. Pain can be severe and is sometimes referred to the abdomen. In bacterial epididymitis, patients may also have fever, nausea, or urinary symptoms. Urethral discharge may be present if the cause is urethritis.

Physical examination reveals swelling, induration, marked tenderness, and sometimes erythema of a portion of or all of the affected epididymis and, sometimes, the adjacent testis. Sepsis is suggested by fever, tachycardia, hypotension, and a toxic appearance.

Diagnosis

• Clinical evaluation

• Sometimes urethral swab and urine culture

Diagnosis is confirmed by finding swelling and tenderness of the epididymis. However, unless findings are clearly isolated to the epididymis, testicular torsion (see p. 2457) must also be considered, particularly in patients < 30 yr; immediate color Doppler ultrasonography is indicated. A GU consultation is indicated if the cause is unclear or the disorder is recurrent.

Urethritis suggests that the cause of epididymitis is a sexually transmitted pathogen, and a urethral swab is sent for gonococcus and chlamydia culture or PCR. Otherwise, the infecting organism usually can be identified by urine culture. Urinalysis and culture are normal in nonbacterial causes.

Treatment

• Antibiotics

• Supportive measures

Treatment consists of bed rest, scrotal elevation (eg, with a jockstrap when upright) to decrease repetitive, minor bumps, scrotal ice packs, anti-inflammatory analgesics, and a broad-spectrum antibiotic such as ciprofloxacin 500 mg po bid or levofloxacin 500 mg po once/day for 21 to 30 days. Alternatively, doxycycline 100 mg po bid or trimethoprim/sulfamethoxazole double-strength (160/800 mg) po bid may by used. If sepsis is suspected, an aminoglycoside such as tobramycin 1 mg/kg IV q 8 h or a 3rd-generation cephalosporin such as ceftriaxone 1 to 2 g once/day IV may be useful until the infecting organism and its sensitivities are known. Abscess and pyocele usually require surgical drainage.

Recurrent bacterial epididymitis secondary to incurable chronic urethritis or prostatitis occasionally can be prevented by vasectomy. An epididymectomy, occasionally done for chronic epididymitis, may not relieve symptoms. Patients who must continuously wear an indwelling urethral catheter are prone to develop recurrent epididymitis and epididymo-orchitis. In such cases, placement of a suprapubic cystostomy or institution of a self-catheterization regimen may be useful.

Treatment of nonbacterial epididymitis includes the above general measures, but antimicrobial therapy is not warranted. Nerve block of the spermatic cord with local anesthesia can relieve symptoms in severe, persistent cases.

Orchitis

Orchitis is infection of the testes, typically with mumps virus. Symptoms are testicular pain and swelling. Diagnosis is clinical. Treatment is symptomatic. Antibiotics are given if bacterial infection is identified.

Isolated orchitis (ie, infection localized to the testes) is nearly always viral in origin, and most cases are due to mumps. Rare causes include congenital syphilis, TB, leprosy, echovirus infection, lymphocytic choriomeningitis, coxsackievirus infection, infectious mononucleosis, varicella, and infection with group B arborviruses. Most bacterial causes also involve the epididymis (epididymo-orchitis—see p. 2455).

Orchitis develops in 20 to 25% of males with mumps; 80% of cases occur in patients < 10 yr. Two thirds of cases are unilateral and one third bilateral. Sixty percent of patients with mumps orchitis develop testicular atrophy in at least one testis. Atrophy is unrelated to fertility or to the severity of the orchitis. The incidence of tumor does not appear to be increased, but unilateral disease diminishes fertility in one fourth of men after unilateral mumps orchitis and in two thirds of men who have had bilateral disease.

Symptoms and Signs

Unilateral mumps orchitis develops acutely between 4 and 7 days after parotid swelling in mumps. In 30% of cases, the disease spreads to the other testis in 1 to 9 days. Pain may be of any degree of severity. In

addition to pain and swelling of the testes, systemic symptoms may develop, such as malaise, fever, nausea, headache, and myalgias. Testicular examination reveals tenderness, enlargement, and induration of the testis and edema and erythema of the scrotal skin.

Other infectious agents cause similar symptoms with speed of onset and intensity related to their pathogenicity.

Diagnosis

• Clinical evaluation and selective testing

History and physical examination usually indicate the diagnosis. Urgent differentiation of orchitis from testicular torsion and other causes of acute scrotal swelling and pain is accomplished with color Doppler ultrasonography. Mumps can be confirmed by serum immunofluorescence antibody testing. Other infectious agents may be identified by urine culture or serology.

Treatment

Supportive care with analgesics and hot or cold packs is sufficient if bacterial infection has been ruled out. Bacterial causes are treated with appropriate antibiotics. Urologic follow-up is recommended.

Peyronie's Disease

Peyronie's disease is fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora, resulting in a deviated and sometimes painful erection.

The disease occurs in adults. The cause is unknown but appears to be similar to that of Dupuytren's contracture. The contracture usually results in deviation of the erect penis to the involved side, occasionally causes painful erections, and may prevent penetration. Fibrosis may extend into the corpus cavernosum, compromising tumescence distally.

Resolution may occur spontaneously over many months. Mild Peyronie's disease that does not cause sexual dysfunction does not warrant treatment.

Treatment

Treatment results are unpredictable. Oral vitamin E and K para-aminobenzoate have had varied success. Surgical removal of the fibrosis and replacement with a patch graft may be successful or may result in further scarring and exaggeration of the defect. A series of local injections of verapamil or high-potency corticosteroids into the plaque may be effective, but oral corticosteroids are not. Ultrasound treatments can stimulate blood flow, which may prevent further scarring. Radiation therapy may decrease pain; however, radiation often worsens tissue damage. To assist penetration, a prosthesis may be implanted but may require a patch procedure to straighten the penis.

Phimosis and Paraphimosis

Phimosis is inability to retract the foreskin; paraphimosis is entrapment of the foreskin in the retracted position.

Phimosis: Phimosis is normal in children and typically resolves by age 5. Treatment is not required in the absence of complications such as balanitis, UTIs, urinary outlet obstruction, unresponsive dermatologic disease, or suspicion of carcinoma.

Three months of betamethasone cream 0.05% bid to tid applied to the tip of the fore-skin and the area touching the glans is often effective. Stretching the foreskin gently with 2 fingers or over an erect penis for 2 to 3 wk with care not to cause paraphimosis is also successful. Circumcision is the preferred surgical option.

In adults, phimosis may result from balanoposthitis or prolonged irritation. Risk of UTI is increased. The usual treatment is circumcision.

Paraphimosis: Paraphimosis can occur when the foreskin is left retracted (behind the glans penis). Retraction may occur during catheterization or physical examination. If the retracted foreskin is somewhat tight, it functions as a tourniquet, causing the glans to swell, both blocking the foreskin from returning to its normal position and worsening the constriction.

Paraphimosis should be regarded as an emergency, because constriction leads quickly to vascular compromise and necrosis. Firm circumferential compression of the glans with the hand may relieve edema sufficiently to allow the foreskin to be restored to its normal position. If this technique is ineffective, a dorsal slit done using a local anesthetic relieves the condition temporarily. Circumcision is then done when edema has resolved.

Testicular Torsion

Testicular torsion is an emergency condition due to rotation of the testis and consequent strangulation of its blood supply. Symptoms are acute scrotal pain and swelling, nausea, and vomiting. Diagnosis is based on physical examination and confirmed by color Doppler ultrasonography. Treatment is immediate manual detorsion followed by surgical intervention.

Anomalous development of the tunica vaginalis and spermatic cord can lead to incomplete fixation of the testis to the tunica vaginalis (bell-clapper deformity—see Fig. 241-1). This anomaly predisposes the testis to twisting on its cord spontaneously or after trauma. The predisposing anomaly is present in about 12% of males. Torsion is most common between the ages of 12 and 18, with a secondary peak in infancy. It is uncommon in men > age 30. It is more common in the left testis.

Symptoms and Signs

Immediate symptoms are rapid onset of severe local pain, nausea, and vomiting,

[**Fig. 241-1.** Abnormal testicular fixation leading to torsion.]

followed by scrotal edema and induration. Fever and urinary frequency may be present. The testis is tender and may be elevated and horizontal. The contralateral testis may also be horizontal because the anatomic defect is usually bilateral. The cremasteric reflex is usually absent on the affected side. Sometimes, torsion can spontaneously resolve and then recur, which may appear to suggest a less acute onset. Usually, however, the onset and resolution of pain is very rapid with each episode.

Diagnosis

• Clinical evaluation

• Often color Doppler ultrasonography

Torsion must be rapidly identified. Similar symptoms result mainly from epididymitis. With epididymitis, pain and swelling are usually less acute and initially localized to the epididymis. However, in both conditions, generalized swelling and tenderness often develop, making it difficult to distinguish torsion from epididymitis. A clinical diagnosis usually is sufficient to proceed to treatment. An equivocal diagnosis may be resolved by immediate imaging if available. Color Doppler ultrasonography of the scrotum is preferred. Radioisotope scrotal scan is also diagnostic but takes longer and is less preferred.

Treatment

• Manual detorsion

• Surgery: Urgently if detorsion is unsuccessful, otherwise electively

Immediate manual detorsion without imaging can be attempted on the initial examination; its success is variable. Because testes usually rotate inward, for detorsion the testis is rotated in an outward direction (eg, for the left testis, detorsion is clockwise when viewed from the front—underneath the testis). More than one rotation may be needed to resolve the torsion; pain relief guides the procedure. If detorsion fails, immediate surgery is indicated, because exploration within a few hours offers the only hope of testicular salvage. Testicular salvage drops rapidly from 80 to 100% at 6 to 8 h to near zero at 12 h. Fixation of the contralateral testis is also done to prevent torsion on that side. When manual detorsion is successful, bilateral testicular fixation is done electively.

Urethral Stricture

Urethral stricture is scarring that obstructs the anterior urethral lumen.

Urethral stricture can be congenital (see p. 2986) or acquired. Anything that damages the urethral epithelium or corpus spongiosum can cause acquired stricture. The most common cause is trauma, such as straddle injury and occasionally iatrogenic injury (eg, after traumatic endoscopy). Less common causes may include lichen sclerosis and urethritis (usually chronic or untreated). Often strictures are idiopathic.

Symptoms and Signs

Symptoms may not develop until the urethral lumen has been decreased considerably. Strictures may cause a double-stream, obstructive voiding symptoms, or recurrent UTIs (including prostatitis). A urethral diverticulum may develop, sometimes accompanied by abscess formation and, rarely, a fistula with extravasation of urine into the scrotum and perineum.

Diagnosis

• Retrograde urethrography or cystoscopy

The diagnosis is usually suspected when urethral catheterization is difficult. It should also be considered in males with gradual onset of obstructive symptoms or recurrent UTIs, particularly if they have risk factors or are young. Diagnosis is usually by retrograde urethrography or cystoscopy.

Treatment

Treatment is determined by the type of obstruction. Often, dilation or endoscopy (internal urethrotomy) is done. However, with certain types of strictures (eg, complicated or recurrent strictures), dilation and endoscopy should be avoided; daily self-catheterization may be indicated. Open urethroplasty may be indicated if the stricture is localized and causes recurrent problems.

Chapter 242. Benign Prostate Disease

Introduction

(Prostate Cancer is discussed on p. 2470.)

The prostate can be affected by hyperplasia, infection, and cancer. The normal prostate is a walnut-sized organ composed of glandular tissue that makes ejaculatory fluid, its only known function. Because prostatic tissue surrounds the urethra, enlargement or other abnormalities may affect urination. The prostate may be examined by digital rectal examination to determine its size, symmetry, texture, and nodularity.

Benign Prostatic Hyperplasia

(Benign Prostatic Hypertrophy)

Benign prostatic hyperplasia (BPH) is nonmalignant adenomatous overgrowth of the periurethral prostate gland. Symptoms are those of bladder outlet obstruction—weak stream, hesitancy, urinary frequency, urgency, nocturia, incomplete emptying, terminal dribbling, overflow or urge incontinence, and complete urinary retention. Diagnosis is based primarily on digital rectal examination and symptoms; cystoscopy, transrectal ultrasonography, urodynamics, or other imaging studies may also be needed. Treatment options include 5α-reductase inhibitors, α-blockers, and surgery.

Using the criteria of a prostate volume > 30 mL and a high American Urological Association Symptom Score (see Table 242-1), the prevalence of BPH in men aged 55 to 74 without prostate cancer is 19%. But if voiding criteria of a maximal urinary flow rate < 10 mL/sec and a postvoid residual urine volume > 50 mL are included, the prevalence is only 4%. Based on autopsy studies, the prevalence of BPH increases from 8% in men aged 31 to 40 to 40 to 50% in men aged 51 to 60 and to > 80% in men > 80.

The etiology is unknown but probably involves hormonal changes associated with aging.

Pathophysiology

Multiple fibroadenomatous nodules develop in the periurethral region of the prostate, probably originating within the periurethral glands rather than in the true fibromuscular prostate (surgical capsule), which is displaced peripherally by progressive growth of the nodules.

As the lumen of the prostatic urethra narrows and lengthens, urine outflow is progressively obstructed. Increased pressure associated with micturition and bladder distention

[**Table 242-1.** American Urological Association Symptom Score for Benign Prostatic Hyperplasia]

can progress to hypertrophy of the bladder detrusor, trabeculation, cellule formation, and diverticula. Incomplete bladder emptying causes stasis and predisposes to calculus formation and infection. Prolonged obstruction, even if incomplete, can cause hydronephrosis and compromise renal function.

Symptoms and Signs

Symptoms include progressive urinary frequency, urgency, and nocturia due to incomplete emptying and rapid refilling of the bladder. Pain and dysuria are usually not present. Decreased size and force of the urinary stream cause hesitancy and intermittency. Sensations of incomplete emptying, terminal dribbling, overflow incontinence, or complete urinary retention may ensue. Straining to void can cause congestion of superficial veins of the prostatic urethra and trigone, which may rupture and cause hematuria. Straining also may acutely cause vasovagal syncope and, over the long term, may cause dilation of hemorrhoidal veins or inguinal hernias.

Some patients present with sudden, complete urinary retention, with marked abdominal discomfort and bladder distention. Retention may be precipitated by any of the following:

• Prolonged attempts to retain urine

• Immobilization

• Exposure to cold

• Use of anesthetics, anticholinergics, sympathomimetics, opioids, or alcohol

Symptoms can be quantitated by the 7-question American Urological Association Symptom Score (see Table 242-1). This score also allows physicians to follow symptom progression: Scores > 10 but < 20 suggest moderate symptoms, and scores > 20 suggest severe symptoms.

On digital rectal examination, the prostate usually is enlarged and nontender, has a rubbery consistency, and in many cases has lost the median furrow. However, prostate size as detected with digital rectal examination may be misleading; an apparently small prostate may cause obstruction. If distended, the urinary bladder may be palpable or percussible during abdominal examination.

Diagnosis

• Digital rectal examination

• Urinalysis and culture

• Prostate-specific antigen level

• Sometimes uroflowmetry and bladder ultrasonography

The lower urinary tract symptoms of BPH can also be caused by other disorders, including infection and prostate cancer. Furthermore, BPH and prostate cancer may coexist. Although palpable prostate tenderness suggests infection, digital rectal examination findings in BPH and cancer often overlap. Although cancer may cause a stony, hard, nodular, irregularly enlarged prostate, most patients with cancer, BPH, or both have a benign-feeling, enlarged prostate. Thus, patients with symptoms or palpable prostatic abnormalities should undergo testing.

Typically, urinalysis and culture are done, and serum prostate-specific antigen (PSA) levels are measured. Men with moderate or severe symptoms of obstruction may also have uroflowmetry (an objective test of urine volume and flow rate) with measurement of postvoid residual volume by bladder ultrasonography. Flow rate < 15 mL/sec suggests obstruction, and postvoid residual volume > 100 mL suggests retention.

Interpreting PSA levels can be complex. The PSA level is moderately elevated in 30 to 50% of patients with BPH, depending on prostate size and degree of obstruction, and is elevated in 25 to 92% of patients with prostate cancer, depending on the tumor volume. Typically, if the PSA level is > 4 ng/mL or if the digital rectal examination indicates an abnormality (other than smooth, symmetric enlargement), then a transrectal biopsy is recommended. For men < 50 or those at high risk of prostate cancer, a lower cutoff (PSA > 2.5 ng/mL) may be used. Other measures, including rate of PSA increase, free-to-bound PSA ratio, and other markers, may be useful (for full discussion of prostate cancer screening and diagnosis, see p. 2470).

Transrectal biopsy is usually done with ultrasound guidance. Transrectal ultrasonography can also measure prostate volume.

Clinical judgment must be used to evaluate the need for further testing. Contrast imaging studies (eg, CT or IVU) are rarely necessary unless obstructive symptoms have been severe and prolonged. Upper urinary tract abnormalities that usually result from bladder outlet obstruction include upward displacement

of the terminal portions of the ureters (fish hooking), ureteral dilation, and hydronephrosis. If an upper tract imaging study is warranted due to pain or elevated serum creatinine level, ultrasonography may be preferred because it avoids radiation and IV contrast exposure.

Treatment

- Avoidance of anticholinergics, sympathomimetics, and opioids
- Use of α-adrenergic blockers (eg, terazosin, doxazosin, tamsulosin, alfuzosin) or 5α-reductase inhibitors (finasteride, dutasteride)
- Transurethral resection of the prostate or a less invasive procedure

Urinary retention: Urinary retention requires immediate decompression. Passage of a standard urinary catheter is first attempted; if a standard catheter cannot be passed, a catheter with a coude tip may be effective. If this catheter cannot be passed, flexible cystoscopy or insertion of filiforms and followers (guides and dilators that progressively open the urinary passage) may be necessary (this procedure should usually be done by a urologist). Suprapubic percutaneous decompression of the bladder may be used if transurethral approaches are unsuccessful.

Drug therapy: For partial obstruction with troublesome symptoms, all anticholinergics, sympathomimetics, and opioids should be stopped, and any infection should be treated with antibiotics. For patients with mild to moderate obstructive symptoms, α-adrenergic blockers (eg, terazosin, doxazosin, tamsulosin, alfuzosin) may improve voiding. The 5α-reductase inhibitors (finasteride, dutasteride) may reduce prostate size, decreasing voiding problems over months, especially in patients with larger (> 30 mL) glands. A combination of both classes of drugs is superior to monotherapy.

Surgery: Surgery is done when patients do not respond to drug therapy or develop recurrent UTI or upper tract dilation. Transurethral resection of the prostate (TURP) is the standard. Erectile function and continence are usually retained, although about 5 to 10% of patients experience some postsurgical problems, most commonly retrograde ejaculation. The incidence of erectile dysfunction after TURP is between 1 and 35%, and the incidence of incontinence is about 1 to 3%. About 10% of men undergoing TURP need the procedure repeated within 10 yr because the prostate continues to grow. Larger prostates (usually > 75 g) require open surgery via a suprapubic or retropubic approach. All surgical methods require postoperative catheter drainage for 1 to 7 days.

Other procedures: Less invasive procedures include microwave thermotherapy, laser ablation, electrovaporization, high-intensity focused ultrasound, transurethral needle ablation, radiofrequency vaporization, and intraurethral stents. The circumstances under which these procedures should be used have not been firmly established, but those done in the physician's office (microwave thermotherapy and radiofrequency procedures) are being more commonly used and do not require use of general or regional anesthesia. Their long-term ability to alter the natural history of BPH is under study.

Prostatitis

(Prostatodynia)

Prostatitis refers to a disparate group of disorders that manifests with a combination of predominantly irritative or obstructive urinary symptoms and perineal pain. Some cases result from bacterial infection of the prostate gland and others, which are more common, from a poorly understood combination of noninfectious inflammatory factors, spasm of the muscles of the urogenital diaphragm, or both. Diagnosis is clinical, along with microscopic examination and culture of urine samples obtained before and after prostate massage. Treatment is with an antibiotic if the cause is bacterial. Nonbacterial causes are treated with warm sitz baths, muscle relaxants, and anti-inflammatory drugs or anxiolytics.

Etiology

Prostatitis can be bacterial or, more commonly, nonbacterial. However, differentiating bacterial and nonbacterial causes can be difficult, particularly in chronic prostatitis.

Bacterial prostatitis can be acute or chronic and is usually caused by typical urinary pathogens (eg, *Klebsiella*, *Proteus*, *Escherichia coli*) and possibly by *Chlamydia*. How these pathogens enter and infect the prostate is unknown. Chronic infections may be caused by sequestered bacteria that antibiotics have not eradicated.

Nonbacterial prostatitis can be inflammatory or noninflammatory. The mechanism is unknown but may involve incomplete relaxation of the urinary sphincter and dyssynergic voiding. The resultant elevated urinary pressure may cause urine reflux into the prostate (triggering an inflammatory response) or increased pelvic autonomic activity leading to chronic pain (see p. 1629) without inflammation.

Classification

Prostatitis is classified into 4 categories (see Table 242-2). These categories are differentiated by clinical findings and by the presence or absence of signs of infection and inflammation in 2 urine samples. The first sample is a midstream collection. Then digital prostate massage is done, and patients void immediately; the first 10 mL of urine constitutes the 2nd sample. Infection is defined by bacterial growth in urine culture; inflammation is defined by the presence of WBCs in urine.

Symptoms and Signs

Symptoms vary by category but typically involve some degree of urinary irritation or obstruction and pain. Irritation is manifested by frequency and urgency, obstruction, a sensation of incomplete bladder emptying, a need to void again shortly after urinating, or nocturia. Pain is typically in the perineum but may be perceived at the tip of the penis, lower back, or testes. Some patients report painful ejaculation.

Acute bacterial prostatitis often causes such systemic symptoms as fever, chills, malaise, and myalgias. The prostate is exquisitely tender and focally or diffusely swollen, boggy, indurated, or a combination. A generalized sepsis syndrome may result, characterized by tachycardia, tachypnea, and sometimes hypotension.

Chronic bacterial prostatitis manifests with recurrent episodes of infection with or without complete resolution between bouts. Symptoms and signs tend to be milder than in acute prostatitis.

Chronic prostatitis/chronic pelvic pain syndrome typically has pain as the predominant complaint, often including pain with ejaculation. The discomfort can be significant and often markedly interferes with quality of life. Symptoms of urinary irritation or obstruction also may be present. On examination, the prostate may be tender but usually is not boggy or swollen.

Asymptomatic inflammatory prostatitis causes no symptoms and is discovered incidentally during evaluation for other prostate diseases when WBCs are present in the urine.

Diagnosis

• Urinalysis

• Prostate massage except possibly in acute bacterial prostatitis

Diagnosis of type I, II, or III is suspected clinically. Similar symptoms can result from urethritis, perirectal abscess, or UTI. Examination is helpful diagnostically only in acute bacterial prostatitis.

Febrile patients with typical symptoms and signs of acute bacterial prostatitis usually have WBCs and bacteria in a midstream urine sample. Prostate massage to obtain a postmassage urine sample is thought to be unnecessary and possibly dangerous in these patients (although danger remains unproved) because bacteremia can be induced. For the same reason, rectal examination should be done gently.

Blood cultures should be obtained in patients who have fever and severe weakness, confusion, disorientation, hypotension, or cool extremities. For afebrile patients, urine samples before and after massage are adequate for diagnosis.

For patients with acute or chronic bacterial prostatitis who do not respond favorably to antibiotics, transrectal ultrasonography and sometimes cystoscopy may be necessary to rule out prostatic abscess or destruction and inflammation of the seminal vesicles.

For patients with types II, III, and IV (non-acute prostatitis) disease, additional tests that can be considered are cystoscopy and urine cytology (if hematuria is also present) and urodynamic measurements (if there is suspicion of neurologic abnormalities or detrusorsphincter dyssynergia).

Treatment

Treatment varies significantly with etiology.

Acute bacterial prostatitis: Nontoxic patients can be treated at home with antibiotics, bed rest, analgesics, stool softeners, and hydration. Therapy with a fluoroquinolone (eg, ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid) is usually effective and can be given until culture and sensitivity results are known. If the clinical response is satisfactory,

[**Table 242-2.** NIH Consensus Classification System for Prostatitis]

treatment is continued for about 30 days to prevent chronic bacterial prostatitis.

If sepsis is suspected, the patient is hospitalized and given broad-spectrum antibiotics IV (eg, ampicillin plus gentamicin) started after the appropriate cultures are taken and continued until the bacterial sensitivity is known. If the clinical response is adequate, IV therapy is continued until the patient is afebrile for 24 to 48 h, followed by oral therapy usually for 4 wk.

Adjunctive therapies include NSAIDs and potentially α-blockers (if bladder emptying is poor) and supportive measures such as sitz baths. Rarely, prostate abscess develops, requiring surgical drainage.

Chronic bacterial prostatitis: Chronic bacterial prostatitis is treated with oral antibiotics such as fluoroquinolones for at least 6 wk. Therapy is guided by culture results; empiric antibiotic treatment for patients with equivocal or negative culture results has a low success rate. Other treatments include anti-inflammatory drugs, muscle relaxants (eg, cyclobenzaprine to possibly relieve spasm of the pelvic muscles), α-adrenergic blockers, and other symptomatic measures, such as sitz baths.

Chronic prostatitis/chronic pelvic pain syndrome: Treatment is difficult and often unrewarding. In addition to considering any and all of the above treatments, anxiolytics (eg, SSRIs, benzodiazepines), sacral nerve stimulation, biofeedback, prostatic massage, and minimally invasive prostatic procedures (such as microwave thermotherapy) have been attempted with varying results.

Asymptomatic inflammatory prostatitis: Asymptomatic prostatitis requires no treatment.

Prostate Abscess

Prostate abscesses are focal purulent collections that develop as complications of acute bacterial prostatitis.

The usual infecting organisms are aerobic gram-negative bacilli or, less frequently, *Staphylococcus aureus*. Urinary frequency, dysuria, and urinary retention are common. Perineal pain, evidence of acute epididymitis, hematuria, and a purulent urethral discharge are less common. Fever is sometimes present. Rectal examination may disclose prostate tenderness and fluctuance, but prostate enlargement is often the only abnormality, and sometimes the gland feels normal.

Diagnosis

• Prostate ultrasonography and possibly cystoscopy

Abscess is suspected in patients with continued or recurrent UTIs despite antimicrobial therapy and persistent perineal pain. Such patients should undergo prostate ultrasonography and possibly cystoscopy. Many abscesses, however, are discovered unexpectedly during prostate surgery or endoscopy; bulging of a lateral lobe into the prostatic urethra or rupture during instrumentation reveals the abscess. Although pyuria and bacteriuria are common, urine may be normal. Blood cultures are positive in some patients.

Treatment

Treatment involves appropriate antibiotics plus drainage by transurethral evacuation or transperineal aspiration and drainage.

Chapter 243. Genitourinary Cancer

Introduction

GU cancers (bladder, penile, prostate, kidney and renal pelvic, testicular, ureteral, and urethral) account for about 40% of cancers in men (primarily as prostate cancer) and 5.6% in women. For discussion of gynecologic cancers, see Ch. 256.

Bladder Cancer

Bladder cancer is usually transitional cell carcinoma. Symptoms include hematuria; later, urinary obstruction can cause pain. Diagnosis is by cystoscopy and biopsy. Treatment is with fulguration, intravesical instillations, surgery, chemotherapy, or a combination.

In the US, > 70,000 new cases of bladder cancer and about 14,700 deaths occur each year. Bladder cancer is the 4th most common cancer among men and is less common among women; male:female incidence is about 3:1. Bladder cancer is more common among whites than blacks, and incidence increases with age.

Risk factors include the following:

- Smoking (the most common risk factor, causing ≥ 50% of new cases)
- Excess phenacetin use (analgesic abuse)
- Long-term cyclophosphamide use
- Chronic irritation (eg, in schistosomiasis or by bladder calculi)
- Exposure to hydrocarbons, tryptophan metabolites, or industrial chemicals, notably aromatic amines (aniline dyes, such as naphthylamine used in the dye industry) and chemicals used in the rubber, electric, cable, paint, and textile industries

Types of bladder cancer include

- Transitional cell carcinomas, which account for > 90% of bladder cancers. Most are papillary carcinomas, which tend to be superficial and well-differentiated and to grow outward; sessile tumors are more insidious, tending to invade early and metastasize.
- Squamous cell carcinomas, which are less common and usually occur in patients with parasitic bladder infestation or chronic mucosal irritation.
- Adenocarcinomas, which may occur as primary tumors or may reflect metastasis from intestinal carcinoma. Metastasis should be ruled out.

In > 40% of patients, tumors recur at the same or another site in the bladder, particularly if tumors are large or poorly differentiated or if several tumors are present. Bladder cancer tends to metastasize to the lymph nodes, lungs, liver, and bone. Expression of tumor gene *p53* may be associated with progression.

In the bladder, carcinoma in situ is high grade but noninvasive and usually multifocal; it tends to recur.

Symptoms and Signs

Most patients present with unexplained hematuria (gross or microscopic). Some patients present with anemia, and hematuria is detected during evaluation. Irritative voiding symptoms (dysuria, burning, frequency) and pyuria are also common at presentation. Pelvic pain occurs with advanced cancer, when a pelvic mass may be palpable.

Diagnosis

• Cystoscopy with biopsy

Bladder cancer is suspected clinically. Urine cytology, which may detect malignant cells, may be done. Cystoscopy (see p. 2317) and biopsy of abnormal areas are usually also done initially because these tests are needed even if urine cytology is negative. The role for urinary antigen tests is still evolving, particularly for low-grade tumors.

For low-stage (superficial, stage T1) tumors, which comprise 70 to 80% of bladder cancers, cystoscopy with biopsy is sufficient for staging. If a tumor is found to invade muscle (≥ stage T2), abdominal and pelvic CT and chest x-ray are done to determine tumor extent and evaluate for metastases. Patients with invasive tumors undergo bimanual examination (rectal examination in men, rectovaginal examination in women) while under anesthesia for cystoscopy and biopsy. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).

Prognosis

Superficial bladder cancer (carcinoma in situ, stage Ta or T1) rarely causes death. For patients with invasion of the bladder musculature, the 5-yr survival rate is about 50%, but adjuvant chemotherapy may improve these results. Generally, prognosis for patients with progressive or recurrent invasive bladder cancer is poor. Prognosis for patients with squamous cell carcinoma or adenocarcinoma of the bladder is also poor, because these cancers are usually highly infiltrative and detected only at an advanced stage.

Treatment

• Transurethral resection and intravesical chemotherapy (for superficial cancers)

• Cystectomy (for invasive cancers)

Superficial cancers: Superficial cancers can be completely removed by transurethral resection or fulguration. Repeated bladder instillations of chemotherapeutic drugs, such as mitomycin C, may reduce risk of recurrence. Doxorubicin and thiotepa are alternatives but rarely used. For carcinoma in situ and other high-grade, superficial, transitional cell carcinomas, immunotherapeutic treatments, such as BCG instillation, alone or in conjunction with interferon alfa-2b, after transurethral resection is generally more effective than chemotherapy instillations.

[**Table 243-1.** Genitourinary Cancer Staging]

Invasive cancers: Tumors that penetrate the muscle (ie, ≥ stage T2) usually require radical cystectomy (removal of bladder and adjacent structures) with concomitant urinary diversion; partial cystectomy is possible for < 5% of patients. Cystectomy is being done with increasing frequency after initial chemotherapy in patients with locally advanced disease. Urinary diversion traditionally involves routing urine through an ileal conduit to an abdominal stoma and collecting it in an external drainage bag. Alternatives such as orthotopic neobladder or continent cutaneous diversion are very common and are appropriate for many, if not most, patients. For both procedures, an internal reservoir is constructed from the intestine. For the orthotopic neo-bladder, the reservoir is connected to the urethra. Patients empty the reservoir by relaxing the pelvic floor muscles and increasing abdominal pressure, so that urine passes through the urethra almost naturally. Most patients maintain urinary control during the day, but some incontinence may occur at night. For continent cutaneous urinary diversion, the reservoir is connected to a continent abdominal stoma. Patients empty the reservoir by self-catheterization at regular intervals throughout the day.

If surgery is contraindicated or refused, radiation therapy alone or with chemotherapy may provide 5-yr survival rates of 20 to 40%. Radiation therapy may cause radiation cystitis or proctitis or bladder contracture.

Patients should be monitored every 3 to 6 mo for progression or recurrence.

Metastatic and recurrent cancers: Metastases require chemotherapy, which is frequently effective but rarely curative unless metastases are confined to lymph nodes. Combination chemotherapy may prolong life in patients with metastatic disease.

Treatment of recurrent cancer depends on clinical stage and site of recurrence and previous treatment. Recurrence after transurethral resection of superficial tumors is usually treated with a 2nd resection or fulguration.

Metastatic Renal Cancer

Nonrenal cancers may metastasize to the kidneys. The most common cancers that metastasize to the kidney are melanomas and solid tumors, particularly lung, breast, stomach, gynecologic, intestinal, and pancreatic. Leukemia and lymphoma may invade the kidneys, which then appear enlarged, often asymmetrically.

Despite extensive interstitial involvement, symptoms are rare, and renal function may not change from baseline. Proteinuria is absent or insignificant, and blood urea and creatinine levels rarely increase unless a complication (eg, uric acid nephropathy, hypercalcemia, bacterial infection) occurs.

Renal metastases are usually discovered during evaluation of the primary tumor or incidentally during abdominal imaging. If there is no known primary tumor, diagnosis proceeds as for renal cell carcinoma (see p. 2474).

Treatment is systemic therapy for the primary tumor, rarely surgery.

Penile Cancer

Most penile cancers are squamous cell carcinomas; they usually occur in elderly uncircumcised men, particularly those with poor local hygiene. Diagnosis is by biopsy. Treatment includes excision.

Human papillomavirus, particularly types 16 and 18, plays a role in etiology. Premalignant lesions include erythroplasia of Queyrat, Bowen's disease, and bowenoid papulosis. Erythroplasia of Queyrat and Bowen's disease progress to invasive squamous cell carcinoma in 5 to 10% of patients; bowenoid papulosis does not appear to do so. The 3 lesions have different clinical manifestations and biologic effects but are virtually the same histologically; they may be more appropriately called intraepithelial neoplasia or carcinoma in situ.

Symptoms and Signs

Most squamous cell carcinomas originate on the glans, in the coronal sulcus, or under the foreskin. They usually begin as a small erythematous lesion and may be confined to the skin for a long time. These carcinomas may be fungating and exophytic or ulcerative and infiltrative. The latter type metastasizes more commonly, usually to the superficial and deep inguinofemoral and pelvic nodes. Metastases to distant sites (eg, lungs, liver, bone, brain) are rare until late in the disease.

Most patients present with a sore that has not healed, subtle induration of the skin, or sometimes a pus-filled or warty growth. The sore may be shallow or deep with rolled edges. Many patients do not notice the cancer or do not report it promptly. Pain is uncommon.

Diagnosis

If cancer is suspected, biopsy is required; if possible, tissue under the lesion should be sampled. CT or MRI helps in staging localized cancer, checking for invasion of the corpora, and evaluating lymph nodes. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).

Treatment

• Excision

Untreated penile cancer progresses, typically causing death within 2 yr. Treated early, penile cancer can usually be cured.

Circumcision or laser ablation may be effective for small, superficial lesions. Partial penectomy is appropriate if the tumor can be completely excised with adequate margins, leaving a penile stump that permits urination and sexual function. Total penectomy is required for large infiltrative lesions. If tumors are high-grade or invade the corpora cavernosa, bilateral ilioinguinal lymphadenectomy is required. The role of radiation therapy has not been established. For advanced, invasive cancer, palliation may include surgery and radiation therapy, but cure is unlikely. Chemotherapy for advanced cancer has had limited success.

Prostate Cancer

Prostate cancer is usually adenocarcinoma. Symptoms are rare until urethral obstruction occurs. Diagnosis is suggested by digital rectal examination or prostate-specific antigen measurement and confirmed by biopsy. Prognosis for most patients with prostate cancer, especially when it is localized or regional, is very good; more men die with prostate cancer than of it. Treatment is with prostatectomy, radiation therapy, palliative measures (eg, hormonal therapy, radiation therapy, chemotherapy), or, for many elderly and even carefully selected younger patients, active surveillance.

Adenocarcinoma of the prostate is the most common nondermatologic cancer in men > 50 in the US. In the US, about 217,750 new cases and about 32,000 deaths (2010 estimates) occur each year. Incidence increases with each decade of life; autopsy studies show prostate cancer in 15 to 60% of men age 60 to 90 yr, with incidence increasing with age. The lifetime risk of being diagnosed with prostate cancer is 1 in 6. Median age at diagnosis is 72, and > 75% of prostate cancers are diagnosed in men > 65. Risk is highest for black men.

Sarcoma of the prostate is rare, occurring primarily in children. Undifferentiated prostate cancer, squamous cell carcinoma, and ductal transitional carcinoma also occur infrequently. Prostatic intraepithelial neoplasia is considered a possible premalignant histologic change.

Hormonal influences contribute to the course of adenocarcinoma but almost certainly not to other types of prostate cancer.

Symptoms and Signs

Prostate cancer usually progresses slowly and rarely causes symptoms until advanced. In advanced disease, hematuria and symptoms of bladder outlet obstruction (eg, straining, hesitancy, weak or intermittent urine stream, a sense of incomplete emptying, terminal dribbling) may appear. Bone pain may result from osteoblastic metastases to bone (commonly pelvis, ribs, vertebral bodies).

Diagnosis

• Screening by digital rectal examination and prostate-specific antigen

• Assessment of abnormalities by transrectal needle biopsy

• Grading by histology

• Staging by CT and bone scanning

Sometimes stony, hard induration or nodules are palpable during digital rectal examination (DRE), but the examination is often normal; induration and nodularity suggest cancer but must be differentiated from

granulomatous prostatitis, prostatic calculi, and other prostate disorders. Extension of induration to the seminal vesicles and lateral fixation of the gland suggest locally advanced prostate cancer. Prostate cancers detected by DRE tend to be large, and > 50% extend through the capsule.

Screening: Most cancers today are found by screening with serum prostate-specific antigen (PSA) levels (and sometimes DRE), commonly done annually in men > 50 yr. Sometimes, annual screening is begun earlier for men at high risk (eg, those with a family history of prostate cancer and blacks). Abnormal findings require histologic confirmation, most commonly by transrectal ultrasound (TRUS)-guided transrectal needle biopsy, which can be done in an office with use of local anesthesia. Hypoechoic areas are more likely to represent cancer. Occasionally, prostate cancer is diagnosed incidentally in tissue removed during surgery for benign prostatic hyperplasia (BPH).

It is still not certain whether screening decreases morbidity or mortality or whether any gains resulting from screening outweigh the decreases in quality of life from treatment of asymptomatic cancers. Most clinicians recommend annual screening. However, most patients with newly diagnosed prostate cancers have a normal DRE, and serum PSA is not ideal as a screening test. Although PSA is elevated in 25 to 92% of patients with prostate cancer (depending on tumor volume), it also is moderately elevated in 30 to 50% of patients with BPH (depending on prostate size and degree of obstruction), in some smokers, and for several weeks after prostatitis. A level of ≥ 4 ng/mL has traditionally been considered an indication for biopsy in men > 50 yr (in younger patients, levels > 2.5 ng/mL probably warrant biopsy because BPH, the most common cause of PSA elevation, is rare in younger men). Although very high levels are significant (suggesting extracapsular extension of the tumor or metastases) and likelihood of cancer increases with increasing PSA levels, there is no cut-off below which there is no risk.

In asymptomatic patients, positive predictive value for cancer is 67% for PSA > 10 ng/mL and 25% for PSA 4 to 10 ng/mL; recent evidence indicates a 15% prevalence of cancer in men ≥ 55 yr with PSA < 4 ng/mL and a 10% incidence with PSA between 0.6 and 1.0 ng/mL. Cancer present in men with lower levels tends to be smaller (often < 1 mL) and of lower grade, although high-grade cancer (Gleason score 7 to 10) can be present at any level of PSA; perhaps 15% of cancers manifesting with PSA < 4 ng/mL are high grade. Although it appears that a cut-off of 4 ng/mL will miss some potentially serious cancers, the cost and morbidity resulting from the increased number of biopsies necessary to find them is unclear.

The decision whether to biopsy may be helped by other PSA-related factors, even in the absence of a family history of prostate cancer. For example, the rate of change in PSA (PSA velocity) should be < 0.75 ng/mL/yr (lower in younger patients). Biopsy is indicated for PSA velocities higher than this.

Assays that determine the free-to-total PSA ratio and complex PSA are more tumor-specific than standard total PSA measurements and may reduce the frequency of biopsies in patients without cancer. Prostate cancer is associated with less free PSA; no standard cut-off has been established, but generally, levels < 10 to 20% warrant biopsy. Other isoforms of PSA and new markers for prostate cancer are being studied. None of these other uses of PSA answers all of the concerns about possibly triggering too many biopsies.

Clinicians should discuss the risks and benefits of PSA testing with patients. Some patients prefer to eradicate cancer at all costs no matter how low the potential for progression and possible metastases is and may prefer annual PSA testing. Others may value quality of life highly and can accept some uncertainty; they may prefer less frequent (or no) PSA testing.

Grading and staging: Grading, based on the resemblance of tumor architecture to normal glandular structure, helps define the aggressiveness of the tumor. Grading takes into account histologic heterogeneity in the tumor. The Gleason score is commonly used. The most prevalent pattern and the next most prevalent pattern are each assigned a grade of 1 to 5, and the two grades are added to produce a total score. Most experts consider a score ≤ 6 to be well differentiated, 7 moderately differentiated, and 8 to 10 poorly differentiated. The lower the score, the less aggressive and invasive is the tumor and the better is the prognosis. For localized tumors, the Gleason score helps predict the likelihood of capsular penetration, seminal vesicle invasion, and spread to lymph nodes. Gleason score, clinical stage, and PSA level together (using tables or nomograms) predict pathologic stage and prognosis better than any of them alone.

Prostate cancer is staged to define extent of the tumor (see Table 243-1). TRUS may provide information for staging, particularly about capsular penetration and seminal vesicle invasion. Patients with clinical stage T1c to T2a tumors, low Gleason score (≤ 7), and PSA < 10 ng/mL usually get no additional staging tests before proceeding to treatment. Radionuclide bone scans are rarely helpful for finding bone metastases (they are frequently abnormal because of trauma of arthritic changes) until the PSA is > 20 ng/mL. CT (or MRI) of the abdomen and pelvis is commonly done to assess pelvic and retroperitoneal lymph nodes if the Gleason score is 8 to 10 and the PSA is over 10 ng/mL, or if the PSA is > 20 ng/mL with any Gleason score. Suspect lymph nodes can be further evaluated by using needle biopsy. An MRI with endorectal coil may also help define the local extent of the tumor in patients with locally advanced prostate cancer (stage T3). The role of IN-111 capromab pendetide scanning for staging is evolving but is certainly not needed for early, localized disease. Elevated serum acid phosphatase—especially the enzymatic assay—correlates well with the presence of metastases, particularly in lymph nodes. However, this enzyme may also be elevated in BPH (and is slightly elevated after vigorous prostatic massage), multiple myeloma, Gaucher's disease, and hemolytic anemia. It is rarely used today to guide treatment or to follow patients after treatment, especially because its value when done as a radioimmune assay (the way it is usually done) has not been established. Reverse transcriptase-PCR assays for circulating prostate cancer cells are being studied as staging and prognostic tools.

Risk of cancer spread is considered low if

• Stage is ≤ T2a

• Gleason score is ≤ 6

• PSA level is ≤ 10 ng/mL

T2b tumor, Gleason score 7, or PSA > 10 ng/mL are considered intermediate risk by most experts. T2c tumor, Gleason score ≥ 8, or PSA > 20 ng/mL (or 2 intermediate risk factors) are generally high risk.

Both acid phosphatase and PSA levels decrease after treatment and increase with recurrence, but PSA is the most sensitive marker for monitoring cancer progression and response to treatment and has virtually replaced acid phosphatase for this purpose.

Prognosis

Prognosis for most patients with prostate cancer, especially when it is localized or regional, is very good. Life expectancy for elderly men with prostate cancer may differ little from age-matched men without prostate cancer, depending on their age and comorbidities. For many patients, long-term local control, or even cure, is possible. Potential for cure, even when cancer is clinically localized, depends on the tumor's grade and stage. Without early treatment, patients with high-grade, poorly differentiated cancer have a poor prognosis. Undifferentiated prostate cancer, squamous cell carcinoma, and ductal transitional carcinoma respond poorly to conventional therapies. Metastatic cancer has no cure. Median life expectancy with metastatic disease is 1 to 3 yr, although some patients live for many years.

Treatment

• For localized cancer within the prostate, surgery or radiation therapy

• For cancer outside of the prostate, palliation with hormonal therapy, radiation therapy, or chemotherapy

• For some men who have low-risk cancers, active surveillance without treatment

Treatment is guided by PSA level, grade and stage of tumor, patient age, coexisting disorders, and life expectancy. The goal of therapy can be

• Active surveillance (formerly known as watchful waiting when used for elderly patients)

• Definitive (aimed at cure)

• Palliative

Most patients, regardless of age, prefer definitive therapy if cancer is potentially curable. However, therapy is palliative rather than definitive if cancer has spread outside the prostate, because cure is unlikely.

Active surveillance: Active surveillance is appropriate for many asymptomatic patients > 70 with low-risk, or possibly even intermediate-risk, localized prostate cancer or if life-limiting disorders coexist; in these patients, risk of death due to other causes is greater than that due to prostate cancer. This approach requires periodic DRE, PSA measurement, and monitoring of symptoms. In healthy younger men with low-risk cancer, active surveillance also requires periodic repeat biopsies. If the cancer progresses, treatment is required. About 30% of patients undergoing active surveillance eventually require therapy. In elderly men, active surveillance results in the same overall survival rate as prostatectomy; however, patients who had surgery have a significantly lower risk of distant metastases and disease-specific mortality.

Definitive therapies: Definitive therapy is aimed at curing prostate cancer. Radical prostatectomy and the minimally invasive techniques of cryotherapy and brachytherapy are used.

Radical **prostatectomy** (removal of prostate with seminal vesicles and regional lymph nodes) is probably best for patients < 70 with a tumor confined to the prostate. Prostatectomy is appropriate for some elderly patients, based on life expectancy, coexisting disorders, and ability to tolerate surgery and anesthesia. Prostatectomy is done through an incision in the lower abdomen. More recently, a robot-assisted laparoscopic approach has been developed that minimizes blood loss and hospital stay but has not been shown to alter outcomes. Complications include urinary incontinence (in about 5 to 10%), bladder neck contracture or urethral stricture (in about 7 to 20%), erectile dysfunction (in about 30 to 100%—heavily dependent on age and current function), and rectal injury (in 1 to 2%). Nerve-sparing radical prostatectomy reduces the likelihood of erectile dysfunction but cannot always be done, depending on tumor stage and location.

Cryotherapy (destruction of prostate cancer cells by freezing with cryoprobes, followed by thawing) is less well established; long-term outcomes are unknown. Adverse effects include bladder outlet obstruction, urinary incontinence, erectile dysfunction, and rectal pain or injury.

Standard external beam **radiation therapy** usually delivers 70 Gy in 7 wk, but this technique has been supplanted by conformal 3-dimensional radiation therapy and by intensity modulated radiation therapy (IMRT), which safely deliver doses approaching 80 Gy to the prostate; data indicate that the rate of local control is higher, especially for high-risk patients. Some decrease in erectile function occurs in at least 40%. Other adverse effects include radiation proctitis, cystitis, diarrhea, fatigue, and possibly urethral strictures, particularly in patients with a prior history of transurethral resection of the prostate. Results with radiation therapy and prostatectomy may be comparable, especially for patients with low pretreatment PSA levels.

Brachytherapy involves the implantation of radioactive seeds into the prostate through the perineum. These seeds emit a burst of radiation over a finite period (usually 3 to 6 mo) and are then inert. Research protocols are examining whether high-quality implants used as monotherapy or implants plus external beam radiation therapy are superior for intermediate-risk patients. Brachytherapy also decreases erectile function, although onset may be delayed and patients may be more responsive to phosphodiesterase type 5 inhibitors than patients whose neurovascular bundles are resected or injured during surgery. Urinary frequency, urgency, and, less often, retention are common but usually subside over time. Other adverse effects include increased bowel movements; rectal urgency, bleeding, or ulceration; and prostatorectal fistulas.

Palliative therapies: For short-term palliation, ≥ 1 drugs may be used, including antiandrogens, chemotherapy drugs (eg, mitoxantrone, estramustine, taxanes), corticosteroids, and ketoconazole; docetaxel plus prednisone is a common combination. Local radiation therapy is usually palliative for

patients with symptomatic bone metastases.

Patients with a locally advanced tumor or metastases may benefit from androgen deprivation by castration, either surgically with bilateral orchiectomy or medically with luteinizing hormone-releasing hormone (LHRH) agonists, such as leuprolide, goserelin, and buserelin, with or without radiation therapy. Reduction in serum testosterone with LHRH agonists equals that with bilateral orchiectomy. All of these treatments cause loss of libido and erectile dysfunction and may cause hot flashes. LHRH agonists may cause PSA levels to increase temporarily. Some patients benefit from adding antiandrogens (eg, flutamide, bicalutamide, nilutamide, cyproterone acetate [not available in US]) for total androgen blockade. Maximal androgen blockade usually refers to LHRH agonists plus antiandrogens, but its benefits appear minimally better than those of an LHRH agonist (or orchiectomy) alone. Another approach is intermittent androgen blockade, which purports to delay emergence of androgen-independent prostate cancer. Total androgen ablation is given until PSA levels are reduced (usually to undetectable levels), then stopped. Treatment is started again when PSA levels rise above a certain threshold, although the ideal threshold is not yet defined. The optimal schedules for treatment and time off treatment have not been determined and vary widely among practitioners. Androgen deprivation may impair quality of life significantly (eg, self-image, attitude toward the cancer and its treatment, energy levels) and cause osteoporosis, anemia, and loss of muscle mass with long-term treatment. Exogenous estrogens are rarely used because they have a risk of cardiovascular and thromboembolic complications. There is no standard therapy for hormone-refractory prostate cancer.

Angiogenesis inhibitors (eg, thalidomide, endostatin), matrix metalloproteinase inhibitors, and cytotoxic and biologic drugs (eg, genetically designed vaccines, antisense therapy, monoclonal antibodies) are being studied and may provide palliation and prolong survival, but their superiority over corticosteroids alone has not been proved. Sipuleucel-T, an autologous cellular immunotherapy drug, is now available for some men with advanced prostate cancer.

For high-grade tumors that extend beyond the prostatic capsule, several treatment protocols exist. Chemotherapy, with or without hormonal therapy, is used before surgery in some protocols and along with radiation therapy in others. Chemotherapy regimens vary by center and trial.

Renal Cell Carcinoma

(Hypernephroma; Adenocarcinoma of the Kidneys)

Renal cell carcinoma (RCC) is the most common renal cancer. Symptoms appear late and include hematuria, flank pain, a palpable mass, and FUO. Diagnosis is by CT or MRI and occasionally by biopsy. Treatment is with surgery for early disease and targeted therapy, an experimental protocol, or palliative therapy for advanced disease.

RCC, an adenocarcinoma, accounts for 90 to 95% of primary malignant renal tumors. Less common primary renal tumors include transitional cell carcinoma, Wilms' tumor (most often in children), and sarcoma.

In the US, about 58,000 cases of RCC and pelvic tumors and 13,000 deaths occur each year. RCC occurs slightly more often in men (male:female incidence is about 3:2). People affected are usually between 50 and 70 yr. Risk factors include the following:

- Smoking, which doubles the risk (in 20 to 30% of patients)
- Obesity
- Excess use of phenacetin
- Acquired cystic kidney disease in dialysis patients
- Exposure to certain radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products

• Some familial syndromes, particularly von Hippel-Lindau disease

RCC can trigger thrombus formation in the renal vein, which occasionally propagates into the vena cava. Tumor invasion of the vein wall is uncommon. RCC metastasizes most often to the lymph nodes, lungs, adrenal glands, liver, and bone.

Symptoms and Signs

Symptoms usually do not appear until late, when the tumor may already be large and metastatic. Gross or microscopic hematuria is the most common manifestation, followed by flank pain, FUO, and a palpable mass. Sometimes hypertension results from segmental ischemia or pedicle compression. Paraneoplastic syndromes occur in 20% of patients. Polycythemia can result from increased erythropoietin activity. However, anemia may also occur. Hypercalcemia is common and may require treatment (see p. 847). Thrombocytosis, cachexia, or secondary amyloidosis may develop.

Diagnosis

• CT with contrast or MRI

Most often, a renal mass is detected incidentally during abdominal imaging (eg, CT, ultrasonography) done for other reasons. Otherwise, diagnosis is suggested by clinical findings and confirmed by abdominal CT before and after injection of a radiocontrast agent or by MRI. A renal mass that is enhanced by radiocontrast strongly suggests RCC. CT and MRI also provide information about local extension and nodal and venous involvement. MRI provides further information about extension into the renal vein and vena cava and has replaced inferior vena cavography. Ultrasonography and IVU may show a mass but provide less information about the characteristics of the mass and extent of disease than do CT or MRI. Often, nonmalignant and malignant masses can be distinguished radiographically, but sometimes surgery is needed for confirmation. Needle biopsy does not have sufficient sensitivity when findings are equivocal; it is recommended only when there is an infiltrative pattern instead of a discrete mass, when the renal mass may be a metastasis from another known cancer, or sometimes to confirm a diagnosis before chemotherapy for metastases.

Three-dimensional CT, CT angiography, or magnetic resonance angiography is used before surgery, particularly before nephronsparing surgery, to define the nature of RCC, to more accurately determine the number of renal arteries present, and to delineate the vascular pattern. These imaging techniques have replaced aortography and selective renal artery angiography.

A chest x-ray and liver function tests are essential. If chest x-ray is abnormal, chest CT is done. If alkaline phosphatase is elevated, bone scanning is needed. Serum electrolytes, BUN, creatinine, and Ca are measured. BUN and creatinine are unaffected unless both kidneys are diseased.

Staging: Information from the evaluation makes preliminary staging possible. Robson's system is still used in the US, but the TNM (tumor, node, metastasis) system is more precise and has almost completely replaced it (see Table 243-1). At diagnosis, RCC is localized in 45%, locally invasive in about 33%, and spread to distant organs in 25%.

Prognosis

Five-year survival rates range from 95% for the American Joint Committee on Cancer (AJCC) stage grouping I (T1 N0 M0) to 20% for stage grouping IV (T4 with any N or M; or N2 with any T or M; or M1). Prognosis is poor for patients with metastatic or recurrent RCC because treatments are usually ineffective for cure, although they may be useful for palliation.

Treatment

• For early RCC, surgical treatment

• For advanced RCC, palliative therapies or experimental protocols

Curative treatments: Radical nephrectomy (removal of kidney, adrenal gland, perirenal fat, and Gerota's fascia) is standard treatment for localized RCC and provides a reasonable chance for cure. Results with open or laparoscopic procedures are comparable. Nephron-sparing surgery (partial nephrectomy) is possible and appropriate for many patients, even in patients with a normal contralateral kidney if the tumor is < 4 cm. Nonsurgical destruction of renal tumors via freezing (cryosurgery) or thermal energy (radiofrequency ablation) is being done in highly selected patients, but long-term data about efficacy and indications are not yet available.

For tumors involving the renal vein and vena cava, surgery may be curative if no nodal or distant metastases exist.

If both kidneys are affected, partial nephrectomy of one or both kidneys is preferable to bilateral radical nephrectomy if technically feasible.

Radiation therapy is no longer combined with nephrectomy.

Palliative treatments: Palliation can include nephrectomy, tumor embolization, and possibly external beam radiation therapy. Resection of metastases offers palliation and, if limited in number, prolongs life in some patients, particularly those with a long interval between initial treatment (nephrectomy) and development of metastases. Although metastatic RCC is traditionally characterized as radioresistant, radiation therapy can be palliative when metastatic in bone.

For some patients, drug therapy reduces tumor size and prolongs life. About 10 to 20% of patients respond to interferon alfa-2b or IL-2, although the response is long-lasting in < 5%. Five new targeted therapies have shown efficacy for advanced tumors: sunitinib, sorafenib, and pazopanib (tyrosine kinase inhibitors) and temsirolimus and everolimus, which inhibit the mammalian target of rapamycin (mTOR). Other treatments are experimental. They include stem cell transplantation, other inter-leukins, antiangiogenesis therapy (eg, bevacizumab, thalidomide), and vaccine therapy. Traditional chemotherapeutic drugs, alone or combined, and progestins are ineffective. Cytoreductive nephrectomy before systemic therapy, or as a delayed surgical procedure to remove the primary tumor after response in the metastases, is commonly done in patients healthy enough to undergo it.

Renal Pelvic and Ureteral Cancers

Cancers of the renal pelvis and ureters are usually transitional cell carcinomas (TCCs) and occasionally squamous cell carcinomas. Symptoms include hematuria and sometimes pain. Diagnosis is by CT, cytology, and sometimes biopsy. Treatment is surgery.

TCC of the renal pelvis accounts for about 7 to 15% of all kidney tumors. TCC of the ureters accounts for about 4% of upper tract tumors. Risk factors are the same as those for bladder cancer. Also, inhabitants of the Balkans with endemic familial nephropathy are inexplicably predisposed to develop upper tract TCC.

Symptoms and Signs

Most patients present with hematuria; dysuria and frequency may occur if the bladder also is involved. Colicky pain may accompany obstruction (see p. 2366). Uncommonly, hydronephrosis results from a renal pelvic tumor.

Diagnosis

• Ultrasonography or CT with contrast

• Cytology or histology

In patients with unexplained urinary tract symptoms, typically ultrasonography or CT with contrast is done. If the diagnosis cannot be excluded, cytologic or histologic analysis is done for confirmation.

Ureteroscopy is done when biopsy of the upper tract is needed or when urine cytology is positive but no source of the malignant cells is obvious. Abdominal and pelvic CT and chest x-ray are done to determine tumor extent and to check for metastases. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).

Prognosis

Prognosis depends on depth of penetration into or through the uroepithelial wall, which is difficult to determine. Likelihood of cure is > 90% for patients with a superficial, localized tumor but is 10 to 15% for those with a deeply invasive tumor. If tumors penetrate the wall or distant metastases occur, cure is unlikely.

Treatment

• Excision or ablation

• Posttreatment surveillance with cystoscopy

Usual treatment is radical nephroureterectomy, including excision of a cuff of bladder. Partial ureterectomy is indicated in some carefully selected patients (eg, patients with a distal ureteral tumor, decreased renal function, or a solitary kidney). Laser fulguration for accurately staged and adequately visualized renal pelvic or low-grade ureteral tumors is sometimes possible. Occasionally, a drug, such as mitomycin C or BCG, is instilled. However, efficacy of laser therapy and chemotherapy has not been established.

Periodic cystoscopy is indicated because renal pelvic and ureteral cancers tend to recur in the bladder, and such recurrence, if detected at an early stage, may be treated by fulguration, transurethral resection, or intravesical instillations. Management of metastases is the same as that for metastatic bladder cancer.

Testicular Cancer

Testicular cancer begins as a scrotal mass, which is usually not painful. Diagnosis is by ultrasonography. Treatment is with orchiectomy and sometimes lymph node dissection, radiation therapy, chemotherapy, or a combination, depending on histology and stage.

Testicular cancer is the most common solid cancer in males aged 15 to 35, with about 8500 cases annually. Incidence is 2.5 to 20 times higher in patients with cryptorchidism. This excess risk is decreased or eliminated if orchiopexy is done before age 10 yr. Cancer can also develop in the contralateral normally descended testis. The cause of testicular cancer is unknown.

Most testicular cancers originate in primordial germ cells. Germ cell tumors are categorized as seminomas (40%) or nonseminomas (tumors containing any nonseminomous elements). Nonseminomas include teratomas, embryonal carcinomas, endodermal sinus tumors (yolk sac tumors), and choriocarcinomas. Histologic combinations are common; eg, teratocarcinoma contains teratoma plus embryonal carcinoma. Functional interstitial cell carcinomas of the testis are rare.

Even patients with apparently localized tumors may have occult nodal or visceral metastases. For example, almost 30% of patients with nonseminomas will relapse with nodal or visceral metastases if they undergo no treatment after orchiectomy (surveillance). Risk of metastases is highest for choriocarcinoma and lowest for teratoma.

Tumors originating in the epididymis, testicular appendages, and spermatic cord are usually benign fibromas, fibroadenomas, adenomatoid tumors, and lipomas. Sarcomas, most commonly rhabdomyosarcoma, occur occasionally, primarily in children.

Symptoms and Signs

Most patients present with a scrotal mass, which is painless or sometimes associated with dull, aching

pain. In a few patients, hemorrhage into the tumor may cause acute local pain and tenderness. Many patients discover the mass themselves after minor scrotal trauma.

Diagnosis

• Ultrasonography for scrotal masses

• Exploration if testicular mass present

• Staging by abdominal, pelvic, and chest CT as well as tissue examination

Many patients discover the mass themselves during self-examination. Monthly self-examination should be encouraged among young men.

The origin and nature of scrotal masses must be determined accurately because most testicular masses are malignant, but most extratesticular masses are not; distinguishing between the two during physical examination may be difficult. Scrotal ultrasonography can confirm testicular origin. If a testicular mass is confirmed, serum markers α-fetoprotein and β-human chorionic gonadotropin should be measured and a chest x-ray taken. Then, inguinal exploration is indicated; the spermatic cord is exposed and clamped before the abnormal testis is manipulated.

If cancer is confirmed, abdominal, pelvic, and chest CT is needed for clinical staging using the standard TNM (tumor, node, metastasis) system (see Table 243-1). Tissue obtained during treatment (usually radical inguinal orchiectomy) helps provide important histopathologic information, particularly about the proportion of histologic types and presence of intratumoral vascular or lymphatic invasion. Such information can predict the risk of occult lymph node and visceral metastases. Patients with nonseminomas have about a 30% risk of recurrence despite normal x-rays and serum markers and having what appears to be localized disease. Seminomas recur in about 15% of such patients.

Prognosis

Prognosis depends on histology and extent of the tumor. The 5-yr survival rate is > 95% for patients with a seminoma or nonseminoma localized to the testis or with a nonseminoma and low-volume metastases in the retroperitoneum. The 5-yr survival rate for patients with extensive retroperitoneal metastases or with pulmonary or other visceral metastases ranges from 48% (for some nonseminomas) to > 80%, depending on site, volume, and histology of the metastases, but even patients with advanced disease at presentation may be cured.

Treatment

• Radical inguinal orchiectomy

• Radiation therapy for seminomas

• Usually retroperitoneal lymph node dissection for nonseminomas

Radical inguinal orchiectomy is the cornerstone of treatment and helps provide important diagnostic information; it also helps formulate the subsequent treatment plan.

Radiation therapy: Standard treatment for seminoma after unilateral orchiectomy is radiation therapy, usually 20 to 40 Gy (higher dose is used for patients with a nodal mass) to the para-aortic regions up to the diaphragm. The ipsilateral ilioinguinal region is no longer routinely treated. Occasionally, the mediastinum and left supraclavicular regions are also irradiated, depending on clinical stage.

Lymph node dissection: For nonseminomas, many experts consider standard treatment to be retroperitoneal lymph node dissection. For clinical stage 1 tumors in patients who have no prognostic factors that predict relapse, an alternative is active surveillance (frequent serum marker measurements, chest x-rays, CT). Intermediate-sized retroperitoneal nodal masses may require retroperitoneal lymph

node dissection and chemotherapy (eg, bleomycin, etoposide, cisplatin), but the optimal sequence is undecided.

Lymph node dissection is done laparoscopically at some centers. The most common adverse effect of lymph node dissection overall is failure to ejaculate. However, a nerve-sparing dissection is often possible, particularly for early-stage tumors, which usually preserves ejaculation.

Chemotherapy: Nodal masses > 5 cm, lymph node metastases above the diaphragm, or visceral metastases require initial platinum-based combination chemotherapy followed by surgery for residual masses. Such treatment commonly controls the tumor long term. Fertility is often impaired, but no risk to the fetus has been proved if pregnancy does occur.

Supportive measures: A cosmetic testicular prosthesis may be placed during orchiectomy. Silicone prostheses are not widely available because of the problems with silicone breast implants. However, saline implants have been developed.

For men who wish to retain reproductive capacity, sperm banking is potentially available in anticipation of radiation therapy or chemotherapy.

Surveillance: Surveillance is appropriate for some patients, although many clinicians do not offer this option because it requires rigorous follow-up protocols and excellent patient compliance to be safe. It is more commonly offered to patients at low risk of relapse. High-risk patients usually get retroperitoneal lymph node dissections or, in some centers, 2 courses of chemotherapy after orchiectomy instead of surgery.

Recurrences: Nonseminoma recurrences are usually treated with chemotherapy, although delayed retroperitoneal lymph node dissection may be appropriate for some patients with nodal relapse and no evidence of visceral metastases. Surveillance is not used as often for seminomas because the morbidity of 2 wk of radiation therapy is so low and the results in preventing late relapse so high that there is less reason to try to avoid treatment.

Urethral Cancer

Urethral cancer is rare and occurs in both sexes; it may be squamous or transitional cell carcinoma or, occasionally, adenocarcinoma.

Most patients are age ≥ 50. Certain strains of human papillomavirus have been implicated in certain cases. Urethral tumors invade adjacent structures early and thus tend to be advanced when diagnosed. External groin or pelvic (obturator) lymph nodes are usually the first sites of metastasis.

Symptoms and Signs

Most women present with hematuria and obstructive voiding symptoms or urinary retention. Most have a history of urinary frequency or urethral syndrome (hypersensitivity of the pelvic floor muscles). Most men present with symptoms of urethral stricture; only a few present with hematuria or a bloody discharge. Sometimes if the tumor is advanced, a mass is felt.

Diagnosis

Diagnosis is suggested clinically and confirmed by cystourethroscopy. Biopsy may be required to differentiate urethral carcinoma, prolapse, and caruncle. CT or MRI is used for staging.

Prognosis

Prognosis depends on the precise location in the urethra and extent of the cancer, particularly depth of invasion. The 5-yr survival rates are > 60% for patients with distal tumors and 10 to 20% for patients with proximal tumors. Recurrence rate is > 50%.

Treatment

• Usually excision or ablation

For superficial or minimally invasive distal tumors in the anterior urethra, treatment is with surgical excision, radiation therapy (interstitial or a combination of interstitial and external beam), fulguration, or laser ablation. Larger and more deeply invasive anterior tumors and proximal tumors in the posterior urethra require multimodal therapy with radical surgery and urinary diversion, usually in combination with radiation therapy. Surgery includes bilateral pelvic and sometimes inguinal lymph node dissection, often with removal of part of the symphysis pubis and inferior pubic rami. The value of chemotherapy, which is sometimes used, has not been established.