Genitourinary System Disorders

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NEOPLASTIC DISEASES

BLADDER CANCER

Definition

Cancer arising in the urinary bladder is a carcinoma of urothelial (transitional cell) origin in the United States and Europe (90% of cases). Less frequently, urothelial carcinomas may originate in the renal pelvis, ureter, or urethra. In other parts of the world, bladder carcinomas of nonurothelial origin are more common.
Who Should Be Suspected?

Suspected patients are older than age 40 years, more commonly males with a history of cigarette smoking, who present with hematuria (painless, intermittent, grossly visible, and present throughout micturition), or irritative voiding symptoms (frequency, urgency, dysuria) that suggest carcinoma in situ (CIS) of the bladder.

The association of pain with bladder cancer (located to the flank; suprapubic, hypogastric, and perineal; abdominal or right upper quadrant areas; bone pain; or headache/disordered cognitive function) can be signs of locally advanced or metastatic disease. Constitutional symptoms (fatigue, weight loss, anorexia, failure to thrive) are usually signs of advanced or metastatic disease and carry a poor prognosis.

The definitive diagnosis and staging of bladder cancer are by cystoscopy, beginning with a baseline evaluation of the bladder and uninvolved mucosa to record the number, size, location, appearance, and growth type (papillary or solid) of all lesions observed. Visible lesions can be biopsied or resected for histologic analysis.

Laboratory Findings

Urinalysis: A positive dipstick test (detecting one to two red cells per high-power field [HPF]) should be confirmed by microscopic analysis (below). Infection should be ruled out by a urine culture prior to further workup of hematuria.

Urine sediment: Hematuria is significant if there are greater than three red cells per HPF, present throughout micturition. The presence of dysmorphic red cells or casts suggests a glomerular origin, whereas normally formed red cells likely originate from infections, tumors, or obstructions/calculi. The specimen should be maintained at room temperature and examined within 30 minutes of collection.

Urinary cytology: Urine cytologic analysis by fluorescence in situ hybridization (e.g., UroVysion™ FISH) can be a useful noninvasive aid both in the primary diagnosis of urothelial carcinoma and in monitoring tumor recurrence (occurring in about 70% of cases after initial treatments). UroVysion™ FISH is designed to detect certain numerical chromosomal abnormalities commonly associated with urothelial carcinoma (either amplifications of chromosomes 3, 7, and 17 or deletions of the 9p21 locus).

Urine biomarkers: Several urine-based biomarkers have been approved for diagnosis or surveillance of patients with a history of the disease. However, their sensitivity is low, and their use is not recommended for an initial workup of a suspected case.

Limitations on Interpretation of the UroVysion™ FISH Test for Bladder Cancer

A positive result in the absence of clinical evidence of urothelial bladder cancer may indicate urothelial malignancies of other organs along the GU tract (kidney, ureter, prostate, or urethra).

A negative result in the presence of other signs or symptoms of urothelial carcinoma may suggest a false-negative test.
Suggested Readings

PROSTATE CANCER

Definition
- Prostate cancer is an adenocarcinoma of the prostate gland, most commonly occurring in the peripheral zone. There is a close association of the cancer with small clumps of cancer cells—carcinoma in situ or prostatic intraepithelial neoplasia (PIN)—although it has not been proven that PIN is the cancer precursor.
- Prostate cancer is generally so indolent that most men die of other causes before the disease becomes clinically advanced. However, globally it is the sixth leading cause of cancer deaths in men (second leading cause in the United States and first in the United Kingdom).

Who Should Be Suspected?
- Prostate cancer tends to develop in men over age 50. In the early stage of the disease, most men have no symptoms directly linked to the cancer, but because the gland surrounds the prostatic urethra, changes in urinary function can occur with disease progression.
- As a presenting symptom, a change in urinary function (frequency, urgency, nocturia, hesitancy) is the most common, but benign prostatic hyperplasia (BPH) figures into the differential diagnosis and is usually the cause.
- Hematuria and hematospermia are uncommon symptoms but, if present, also are more likely to be caused by BPH. However, if occurring in older men, prostate cancer should be included in the differential diagnosis.
- Bone pain, often in the vertebrae, pelvis, or ribs, if present, would indicate metastatic disease.

Early Detection
- The two methods for early detection of suspected prostate cancer are the digital rectal examination for asymmetric areas of induration or nodules on the posterior and lateral aspects of the prostate gland and measurement of serum prostate-specific antigen (PSA). About 20% of early detections occur through a suspicious digital rectal examination and the remaining 80% through a suspicious PSA test. A definitive diagnosis of prostate cancer by either method of early detection is established by a positive biopsy.
- Screening of unsuspected cases for prostate cancer via the PSA test is controversial. Because of the low specificity of elevated PSA levels for prostate cancer versus BPH or prostatitis, the benefits of screening are outweighed by the harms of unnecessary treatment. Screening is not recommended by the U.S. Preventive Services Task Force (Grade “D,” 2012) and the Centers for
Laboratory Findings

- PSA testing: PSA levels normally correlate with age and prostate size, averaging 1 ng/mL for men under age 50 and 3 ng/mL for men over age 60. A value of 4.0 ng/mL is widely used as a cutoff for prostate cancer. There are two effective methods of enhancing the specificity of the PSA test—use of an age-based reference range and calculation of the free versus total PSA ratio.
  - Age-based reference range: A PSA reference range based on age should be calculated for each laboratory performing PSA testing.
  - PSA free versus total ratio: The risk of prostate cancer is increased if the ratio of free to total PSA is <25%.
  - PSA velocity: An annual rate of change in the PSA level >2.0 ng/mL, while not an effective screening test, offers value in assessing preoperative mortality risk.

Suggested Readings


CARCINOMA OF THE RENAL PELVIS AND URETER

Definition

- Carcinomas of the renal pelvis and ureter are primary tumors of urothelial (transitional cell) origin. Primary tumors arising in the renal pelvis include urothelial carcinomas (>90% of cases), squamous cell carcinomas (8%), and adenocarcinomas (rare).

Who Should Be Suspected?

- Individuals with carcinoma of the renal pelvis or ureter are most likely to have hematuria (70–95% of cases) or flank pain (8–40%) stemming from obstruction of the ureter or ureteropelvic junction by a tumor mass. Other types of urinary tract symptoms (bladder irritation, constitutional symptoms) are less likely to be seen at diagnosis (<10%). Calculi or chronic infection may precede the squamous cell carcinomas.
Laboratory Findings
- Urine cytology: Examination of urinary sediment for malignant cells is a less reliable method for diagnosis of these cases than for bladder cancers because of the poor yield of low-grade tumors and the likelihood of synchronous bladder cancer (40–50% of cases).

Suggested Readings

LEUKOPLAKIA OF THE RENAL PELVIS
Definition
- Leukoplakia of the renal pelvis is a visualized grayish patch observed on the mucosal surface epithelium of the renal pelvis (part of the kidney urothelium) and represents metaplastic squamous plaque (squamous metaplasia and keratinization).

Who Should Be Suspected?
- Candidates are typically middle-aged individuals with recurrent episodes of renal or ureteric colic. In 90% of cases, the lesion is unilateral.

Laboratory Findings
- Urine cytology (cell block or Pap smear): The finding of sheets of desquamated keratinized epithelial cells in urine during an attack of renal colic is pathognomonic.
- Flow cytometry (DNA): High-grade (aneuploid) tumors can be detected in >90% of cases.

Suggested Readings

DISORDERS
BENIGN PROSTATIC HYPERPLASIA (BPH)
Definition
- BPH is enlargement of the prostate resulting from hyperplasia of prostatic stromal and epithelial cells, compressing the periurethral region of the prostate and causing partial or complete obstruction of the urethra.
Who Should Be Suspected?

Candidates are men, generally older than 30 years, with moderate to severe lower urinary tract symptoms (frequency, nocturia, hesitancy, urgency, weak stream) that gradually progress with time.

A history and physical examination should include a digital rectal examination of the prostate. A urine culture and urinalysis for hematuria should be undertaken to rule out other or more serious disorders that could cause symptoms similar to those of BPH (urinary tract infection, bladder calculi, prostatitis, prostate cancer, or bladder cancer). On digital rectal examination, symmetric enlargement and firmness of the prostate are typical of BPH, whereas asymmetric areas are suggestive of prostate cancer.

Laboratory Findings

Serum prostate-specific antigen (PSA): In 20% of BPH patients, serum PSA may be increased from the widely used prostate cancer cutoff value of 4.0–10 ng/mL. In fact, BPH is a more common cause of elevated PSA levels than is prostate cancer.

Serum creatinine: While not recommended by the American Urological Association in the management of patients with BPH, a high serum creatinine value may suggest a bladder outlet obstruction or underlying renal or prerenal disease and an increased risk for post–prostate surgery complications and mortality.

Suggested Readings


CALCULI

Definition

A renal calculus (kidney stone) is a solid concretion/crystalline aggregate formed in the kidneys by supersaturation of dietary minerals in the urine, one or more of which nucleate seed crystals. Both the supersaturation and the crystalline aggregation processes are pH dependent.

Calciuli can be classified by their location and chemical composition.

Locations include the kidney (nephrolithiasis), ureter (ureterolithiasis), or bladder (cystolithiasis).

Varieties of chemical composition include calcium containing (primarily calcium oxalate but also calcium phosphate); struvite (magnesium ammonium phosphate); uric acid; and cystine.
Calcium oxalate or calcium phosphate calculi occur in 85% of male and 70% of female patients. Calcium oxalate crystals require an acid environment. Calcium phosphate crystals occur with hypercalciuria, hypocitraturia, and an alkaline environment (Figure 7-1). A comparison of idiopathic causes of hypercalciuria is presented in Table 7-1.

Struvite stones (staghorn calculi), occurring in 10–15% of patients, are generated by UTI urea-splitting bacteria, including Proteus species (>50% of cases; after ruling out Klebsiella, Pseudomonas, Serratia, and Enterobacter), and in patients with persistently alkaline urine. Although not producing symptoms unless inducing urinary tract obstruction or infection, this type of calculus can lead to renal failure over years if present bilaterally. Staghorn calculi should be cultured.

Cystine stones are rare, occurring in patients with homozygous congenital familial cystinuria, and characterized by bilateral obstructive staghorn calculi with associated renal failure.

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**Figure 7–1** Algorithm for diagnosis of renal calculi, as revealed by flank pain, renal colic, hematuria, fever, and urinalysis findings. I, increased; N, normal; PTH, parathyroid hormone; HPT, hyperparathyroidism; HHM, humeral hypercalcemia of malignancy.
In adults, the most common symptom of calculi that obstruct the ureter or renal pelvis is excruciating, intermittent pain that radiates from the flank to the groin or to the genital area and inner thigh. The pain is commonly accompanied by urinary urgency, restlessness, hematuria, sweating, nausea, and vomiting.

The waves or paroxysms of pain usually last 20–60 minutes and is related to the passage of the stone down the ureter and the associated ureteral spasm.

Flank pain is caused by upper ureteral or renal pelvic obstruction, whereas genital pain is caused by lower ureteral obstruction.

The differential diagnosis of patients with flank pain includes renal bleeding, pyelonephritis, ectopic pregnancy, rupture or torsion of an ovarian cyst, dysmenorrhea, intestinal obstruction, diverticulitis, appendicitis, biliary colic and cholecystitis, and herpes zoster. The intestinal and hepatic causes of flank pain are not accompanied by hematuria nor is a herpes zoster infection (which is usually accompanied by a rash).

Precipitating causes in adults with calculi (20–30%) include destructive bone diseases (either destructive, e.g., metastatic tumors; or osteoporotic, e.g., immobilization, Paget disease, or Cushing syndrome); milk-alkali (Burnett) syndrome; hypervitaminosis D; sarcoidosis; RTA-type I (hypercalciuria, highly alkaline urine, normal serum calcium); hyperthyroidism; and gout (25% of primary cases, 40% of cases with marrow-proliferative disorders).

Precipitating causes in children with calculi include infections (13–40%); hypercalciuria (idiopathic but also caused by distal RTA and therapy with furosemide, prednisone, or ACTH); oxaluria (3–13%); uric acid (4%); cystinuria (5–7%); hypocitraturia (10%); xanthine (an inborn error of metabolism); and adenine phosphoribosyltransferase deficiency.

Laboratory Findings

Two 24-hour urine specimens should be collected and tested for daily volume and levels of magnesium, sodium, uric acid, calcium, citrate, and oxalate.

A urine culture should be performed to detect infecting microorganisms.
Urine microscopy should be performed to detect the presence and level of red cells, white cells, urinary casts, and crystals.

Calculi should be collected by urination through a stone screen, for chemical analysis.

- Hematuria: Gross or microscopic, occurs in 80% of symptomatic patients and is the single most definitive predictor of a calculus in patients with unilateral flank pain. However, hematuria is not detected in 10–30% of patients with documented nephrolithiasis.
- Renal function tests: Useful for interpretation of hypercalcemia.
- Crystalluria: Diagnostically useful for cystine crystals (in familial cystinuria) or struvite crystals.
- Cyanide-nitroprusside test: Positive (false positive may occur with sulfur-containing drugs). Calcium oxalate, phosphate, and uric acid should arouse suspicion about possible causes, but they may occur in normal urine.
- Neutrophilia: Suggestive of infection, for example, in the finding of struvite crystals.

**Suggested Readings**


**HEMATURIA**

- **Definition**
  - The term hematuria refers to the microscopic detection in urine of >2 RBCs per high-power field. It should not be confused with hemoglobinuria, a term reserved for the presence of free hemoglobin in urine.
  - Hematuria may be macroscopic (grossly visible as red or brown urine) or microscopic (detectable only by microscopy). It can be classified as glomerular or nonglomerular in origin. Centrifugation allows one to differentiate hematuria (RBCs in sediment) from hemoglobinuria (normal sediment, heme-pigmented supernatant), which can be tested for heme with a urine dipstick.

- **Who Should Be Suspected?**
  - Hematuria is common and, in many patients, particularly young adults, is transient and inconsequential. With increasing age, common causes can include inflammation or infection of the prostate or bladder and calculi. In patients over age 35, hematuria is associated with a higher risk of benign prostatic hyperplasia and renal or GU malignancies.
  - Patients on oral anticoagulants and those with a high international normalized ratio (INR) are at higher risk of hematuria. Even if present in such patients, it is necessary to investigate for alternative source(s) of the condition.
  - Isolated hematuria occurs in patients with calculi, trauma, prostatitis, sickle cell trait or disease, tuberculosis, and *Schistosoma haematobium*
infection. Acute cystitis or urethritis in women can cause gross hematuria. Hypercalciuria and hyperuricosuria are also risk factors for unexplained isolated hematuria.

- **Benign familial or recurrent hematuria** refers to asymptomatic, recurrent hematuria without proteinuria or other laboratory abnormalities. Persistent or recurrent hematuria, even if only microscopic, should be investigated, especially in patients over age 50. Other family members may be affected. The condition may clear spontaneously.

### Laboratory Findings

- The single most important test in the evaluation of hematuria is the microscopic analysis of urine sediment, which can often distinguish glomerular from nonglomerular bleeding.

- Microscopy of centrifuged urinary sediment should be examined under high dry magnification. Note that <3% of normal persons have ≥3 RBC per HPF. RBCs or casts indicate that the blood is of glomerular origin. The most common causes of isolated glomerular hematuria are IgA nephropathy, hereditary nephritis (Alport syndrome), and thin basement membrane disease. The presence of clots rules out a glomerular origin—large thick clots suggest a bladder origin, whereas small stringy clots indicate upper urinary tract disease. The presence of WBCs suggests inflammation or infection.

- The urine dipstick can detect RBCs at a level equivalent to one to two RBCs per HPF, but results in more false-positive tests owing to a number of interfering factors (listed below), and so a positive dipstick test must be confirmed by microscopic examination of the urine. Proteinuria is also detected by dipstick, and a 2+ proteinuria in the presence of microscopic hematuria indicates glomerular disease.

- Immunocytochemical staining for human Tamm-Horsfall protein is positive with >80% of RBCs of renal origin and <13.1% of RBCs of nonrenal origin.

- Imaging studies, urinary cytology, cystoscopy, or occasionally renal biopsy may be indicated in cases of persistent hematuria with no obvious etiology.

### Limitations on the Urine Dipstick Test

- Causes of false-positive results
  - Vaginal bleeding (menstruation)
  - Viral illness
  - Bacteriuria
  - Certain foods (beets, blackberries, rhubarb)
  - Pigmenturia (myoglobin, porphyrin, hemoglobin)
  - Drugs (rifampin, phenolphthalein, iodides, bromides, copper, oxidizing agents, permanganate)
  - Postejaculate semen
  - Red diaper syndrome
  - Trauma
  - Vigorous exercise prior to collection
Disorders

- pH > 9
- Factitious
- Causes of false-negative results
  - Reducing agents (high doses of vitamin C)
  - pH < 5.1

**Suggested Readings**


### HEMOGLOBINURIA

**Definition**

- Hemoglobinuria refers to the presence of free hemoglobin (Hb) in urine. The condition is often associated with hemolytic anemia, wherein intravascular red cell destruction increases levels of free plasma Hb. The excess Hb is filtered by the kidneys and excreted into the urine where it is visibly detected. The renal threshold for hemoglobinuria is 100–140 mg Hb/dL plasma.

- Although free Hb directly passing the glomeruli in the ultrafiltrate is relatively uncommon (usually, RBCs enter the urinary tract and undergo various amounts of lysis), nevertheless, conditions resulting in intravascular hemolysis have the potential of producing hemoglobinuria once all available plasma haptoglobin is bound by Hb. Hb is readily absorbed by the renal proximal tubules as dissociated dimers and catabolized to ferritin. In turn, ferritin is denatured to hemosiderin that can be found in urine in cases of severe, prolonged hemoglobinuria.

**Who Should Be Suspected?**

- Candidates include patients with red urine but no red cells in urinary sediment, especially if there is a history suggesting intravascular hemolysis. The classic patient with hemolysis may have many of the following findings: rapid onset of pallor, anemia, jaundice, a history of pigmented (bilirubin) gallstones, splenomegaly, the presence of circulating spherocytic or fragmented red cells on the peripheral blood smear, and/or a positive direct antiglobulin test (Coombs test).

- Inciting causes of hemoglobinuria fall into several categories:
  - Hemolytic anemias with intravascular hemolysis
    - Paroxysmal nocturnal hemoglobinuria
    - Paroxysmal cold hemoglobinuria
    - Microangiopathic hemolytic anemias (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome), prosthetic heart valves, severely damaged natural valves (especially aortic)
    - Severe autoimmune hemolytic anemias
    - Fava bean sensitivity, G6PD deficiency, and other hemoglobinopathies
    - Severe hereditary spherocytosis
  - Other hematologic crises (e.g., disseminated intravascular coagulation [DIC], incompatible transfusion reactions).
Infections (e.g., Clostridium perfringens [previously known as Clostridium welchii]; E. coli bacteremia from transfused blood; Bartonella bacilliformis, the agent of Oroya fever or Carrion disease).

Parasitemias (e.g., malaria).

Organ damage (e.g., kidney infarction, diabetic acidosis).

Physical or chemical trauma (e.g., strenuous exercise, march hemoglobinuria, thermal burns, infusion or bladder irrigation with hypotonic solutions, naphthalene, sulfa drugs).

Laboratory Findings

The diagnosis of intravascular hemolysis is usually based on the medical history and analysis of blood and urine specimens. A positive dipstick test and the microscopic absence of urine RBCs and RBC casts suggest hemoglobinuria or myoglobinuria.

Serum LDH and haptoglobin: The combination of an increased level of serum LDH and a reduced level of haptoglobin has been shown to be 90% specific for the diagnosis of hemolysis, whereas the combination of a normal serum LDH and a serum haptoglobin >25 mg/dL has been shown to be 92% sensitive for ruling out hemolysis.

Free Hb: In correlation with hemosiderin in the urine sediment, the finding of free Hb in the plasma and/or urine is highly specific for the presence of intravascular hemolysis.

Spectrophotometry: Presence of Hb in both urine and plasma (deoxy Hb highest absorption peak is at 420 nm, with a secondary peak at 580 nm) is indicative of intravascular hemolysis.

Serum conjugated bilirubin and urine urobilinogen: Both are elevated with hemolysis.

Limitations

Causes of false-positive dipstick results

- Delayed processing of hematuria specimen, resulting in hemolysis of RBCs
- Non-Hb urine pigments that may mimic hemoglobinuria (myoglobin, porphyrin)
- Presence of pus, iodides, or bromides

Suggested Readings


HYPEROXALURIAS

Definitions

Primary hyperoxalurias (PHs) are rare inborn errors of glyoxylate metabolism, characterized by the overproduction of oxalate, which is deposited as calcium oxalate in various organs, primarily the kidneys. End-stage renal disease results in a significant number of cases. PH types 1–3 stem from autosomal recessive enzymatic defects in
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- (PH type 1) the hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase, which is involved in the conversion of glyoxylate to glycine (80% of PH cases)
- (PH type 2) the cytosolic glyoxylate reductase/hydroxypyruvate reductase, which is involved in the conversion of glyoxylate to glycolate (10% of PH cases)
- (PH type 3) the mitochondrial 4-hydroxy-2-oxoglutarate aldolase (5% of PH cases)

Secondary hyperoxaluria results from increased enteric absorption of oxalate, most commonly caused by fat malabsorption via the binding of calcium by free fatty acids in the colon. This decreases the amount of calcium available to bind to oxalate for the formation of insoluble calcium oxalate, leaving the free oxalate to be more easily absorbed.

Specific disorders of fat malabsorption result from pancreatic insufficiency, inflammatory bowel disease, bowel resection or jejunoileal or gastric bypass, use of the weight reduction drug orlistat (which causes fat malabsorption by inhibiting gastric and pancreatic lipases), and cystic fibrosis (which causes pancreatic insufficiency and promotes calcium deposition via hypercalciuria).

Secondary hyperoxaluria may also be precipitated by the chronic ingestion of oxalate precursors (e.g., ascorbic acid) or of foods rich in oxalic acid (e.g., rhubarb, parsley, cocoa, nuts, or star fruit [carambola]).

Who Should Be Suspected?

- PH type 1: The age range at diagnosis varies from <1 to >50.
  - Infants (26% of PH type 1 cases) are generally diagnosed younger than 6 months of age with nephrocalcinosis (91%), failure to thrive (22%), urinary tract infection (21%), and end-stage renal disease (ERSD, 14%).
  - Those diagnosed in childhood generally present with symptoms of recurrent urolithiasis and rapidly declining renal function (30%), that is, renal colic, hematuria, and urinary tract infection, although a few will have bilateral obstruction and acute renal failure.
  - Adults are diagnosed either by the occasional calculus formation (30%) or only after failed isolated renal transplant (10%).

Laboratory Findings

- Urinary oxalate: PH type 1 or 2, usually >100 mg/24 hours unless renal function is diminished; secondary disease, usually 50–100 mg/24 hours.
- Molecular genetic testing (PH type 1): Demonstrates the mutation of the alanine:glyoxylate aminotransferase (AGXT) gene.

Suggested Readings

PRIAPISM

Definition

- Priapism is a persistent erection of the penis (or clitoris), lasting at least 4 hours, that is not associated with sexual stimulation or desire. This relatively rare condition can occur in all age groups (although it exhibits a bimodal peak distribution of incidence at ages 5–10 and 20–50) and is especially common in those with sickle cell disease. Classified as either ischemic or non-ischemic, ischemic priapism is a urologic emergency, whereas nonischemic priapism is usually self-limited.

- Ischemic (low flow, anoxic, or venoocclusive) priapism is the most common form of the condition. The prolonged nitric oxide–mediated relaxation and paralysis of cavernosal smooth muscle results in a compartment syndrome with increasing hypoxia and acidosis in the cavernous tissue. Structural damage to the erectile tissue is believed to occur at the microscopic level as early as 4–6 hours after the onset of the erection, with significant structural changes in the cavernous smooth muscle after 12 hours and irreversible damage as early as 24 hours after onset.

- Nonischemic (high flow, arterial, or congenital) priapism usually results from a fistula between the cavernosal artery and the corpus cavernosum. It commonly follows penile or perineal trauma, or blunt trauma (such as from bicycling). It may also stem from a congenital arterial malformation. In any event, nonischemic priapism is not an emergency condition because the cavernous blood is well oxygenated.

- Recurrent (stuttering) priapism is a form of the ischemic condition (usually occurring in men with sickle cell anemia), which begins with erections of short duration (usually during sleep), then persisting on waking, becoming of longer duration, and increasing frequency until transforming into the classical ischemic form.

Who Should Be Suspected?

- Patients typically present with an erection of 2–4 hours in the absence of sexual excitation. The duration may be shorter for patients with recurrent priapism.

- Causes can be classified into seven categories:
  - Thromboembolic disease (sickle cell disease or trait, polycythemia, pelvic thrombophlebitis)
  - Infiltrative diseases (e.g., leukemia, bladder or prostate carcinoma)
  - Penile trauma
  - CNS infection (e.g., syphilis, TB) or spinal cord injury or anesthesia
  - Intracavernous injectables for treatment of erectile dysfunction (papaverine, alprostadil, phentolamine)
  - Other medications: Antihypertensives, antipsychotics (e.g., chlorpromazine, clozapine), antidepressants (especially trazodone), anticoagulants, testosterone, heparin, and recreational drugs (alcohol, cocaine, marijuana, cantharides)
  - Other causes: Prostatitis and retroperitoneal bleeding. Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil) have only rarely been implicated.
Laboratory Findings

- Cavernous blood gas analysis and/or Doppler ultrasonography can be used to distinguish immediately ischemic from nonischemic priapism persisting longer than 4 hours.
- A volume of 3–5 mL is aspirated with a 19- to 21-gauge needle from one side of the corpus cavernosum.
  ▼ The color of ischemic blood will be black, and blood gas analysis will reveal hypoxia, hypercarbia, and acidemia.
  ▼ The color of nonischemic blood will be red, and blood gas analysis will reveal normal levels of oxygen, carbon dioxide, and pH.

Suggested Readings


RETROPERITONEAL FIBROSIS

Definition

- Retroperitoneal fibrosis (formerly Ormond disease) is a rare condition (incidence of 0.1–1.3 per 100,000 for the idiopathic form) characterized by the proliferation of inflammatory and fibrous tissue in the retroperitoneum, often encasing the ureters or abdominal organs and resulting in ureteral blockage.
- The disorder occurs primarily (70% of cases) in idiopathic form among individuals at age 40–60 (70%). There are also secondary forms of the disorder with a variety of identified causes (certain drugs, malignancies, infections, radiation therapy, retroperitoneal hemorrhage, and surgical sequelae).
- The pathogenesis of the disorder is unclear, but two leading theories suggest (each with some evidence) either an exaggerated local inflammatory reaction to aortic atherosclerosis (incited by oxidized low-density lipoprotein) or a manifestation of systemic autoimmune disease.

Who Should Be Suspected?

- Compiling the data from four studies, the most common presenting symptoms are pain in the lower back, abdomen, and/or flank (28–90%); testicular pain (50–64%); fatigue (60%); substantial weight loss (54%); and new-onset hypertension (33–57%). Urinary symptoms (urgency, frequency, and dysuria) are also common. Most patients have renal impairment by the time they are seen for medical attention.

Laboratory Findings

- The diagnostic method of choice is a contrast-enhanced CT scan to visualize the extent of fibrosis, to assess the presence of lymphadenopathy and tumors, and to enable guided biopsy for tissue analysis.
Although there are no biochemical or hematologic markers of the disorder, ureteral obstruction is assessed by measurements of BUN and serum creatinine concentration. Both are usually elevated in correlation with the presence and extent of obstruction.

The inflammatory level of the disorder is assessed by measurement of the erythrocyte sedimentation rate and C-reactive protein, both of which are elevated in the majority of patients at presentation.

Antinuclear antibodies may be found in up to 60% of cases.

Anemia is found in up to 38% of cases.

Suggested Readings

**INFECTIONS**

**URINARY TRACT INFECTIONS***

Urinary tract infections (UTIs) are among the most common infections encountered in both outpatient and inpatient settings.

- **Definitions and Key Concepts**
  - Most UTIs are restricted to infection of the bladder (cystitis), though infection may occur in any area of the urinary tract, from the kidney to urethra.
  - Most UTIs are caused by uropathogenic organisms from the gastrointestinal or vaginal floras that colonize the periurethral mucosa. Organisms are able to ascend through the urethra to the bladder by various mechanisms.
  - Acute cystitis that occurs in healthy (including no history suggestive of urinary tract abnormality), premenopausal, nonpregnant women is classified as uncomplicated. All other UTIs are classified as complicated.
  - Uncomplicated cystitis rarely progresses to severe infection. The goal of antibiotic therapy of uncomplicated cystitis is for amelioration of symptoms.
  - Most UTIs are caused by a single uropathogenic species. Polymicrobial infections may occur in patients with anatomical abnormalities or foreign bodies, but suspect colonization or culture contamination for cultures that yield growth of more than two different species.
  - Etiology: *E. coli* causes >75% of all uncomplicated UTIs. Most other UTIs are caused by other enteric gram-negative bacilli (e.g., *K. pneumoniae* and *P. mirabilis*) and gram-positive cocci (e.g., *Enterococcus* species, *S. saprophyticus*, Group B streptococcus). Resistant organisms (e.g., *C. albicans*, *P. aeruginosa*) are usually associated with nosocomial and health care–related UTIs.
  - Renal tissues may be infected by ascending infection through the ureters or by hematogenous seeding during bacteremia.

*Written by Michael Mitchell, MD.*
Asymptomatic bacteriuria is defined by a urine culture, submitted by a patient without dysuria or other symptoms of UTI, that yields growth of >10⁵ cfu/mL of a single uropathogen. Pregnant women with asymptomatic bacteriuria are at increased risk for developing UTI, including pyelonephritis, and low birth weight infants. Screening for asymptomatic bacteriuria with a routine urine culture at 12–16 weeks of gestation is recommended. Antibiotic treatment significantly reduces the risks associated with asymptomatic bacteriuria in pregnant women. The clinical value of treating asymptomatic bacteriuria in men or in nonpregnant women has not been established. Screening for asymptomatic bacteriuria in these groups is not recommended.

Renal abscess: Most renal abscesses occur in the setting of obstructive pyelonephritis, caused by ascending infection. Predisposing factors include diabetes, renal stones, tumor, neurogenic bladder, and vesicoureteral reflux. Enteric bacilli are implicated most frequently, but polymicrobial infections occur commonly. Renal abscess and perinephric abscess may also occur as a result of hematologic seeding of the renal parenchyma or perirenal fat and are usually caused by S. aureus. Signs and symptoms of renal or perinephric abscess are similar to those of severe pyelonephritis.

Sterile pyuria: Conditions other than acute bacterial UTI should be considered for patients with pyuria (≥10 WBC/HPF) and negative urine culture. Potential causes include infectious conditions (e.g., renal tuberculosis, urethritis/STI, prostatitis, and viral cystitis or genital infection) and noninfectious conditions (e.g., inflammation by exposure to allergen or chemical agent, mechanical irritation due to stone or instrumentation, renal diseases associated with inflammation).

Who Should Be Suspected/Who Should Be Tested?

Risk factors for complicated UTI:
- Pregnancy
- Urinary tract abnormality, including anatomical obstruction, indwelling foreign body, recent surgery, or instrumentation
- Medical conditions, including diabetes, underlying renal disease, immunosuppression, history of complicated UTI, or recent hospitalization

Clinical signs and symptoms
- Cystitis: Dysuria, urgency, frequency, suprapubic pain, hematuria.
- Pyelonephritis: Fever (>38°C), flank pain, costovertebral angle tenderness, nausea, vomiting, malaise. Signs and symptoms of cystitis are common. Patients may present with signs of sepsis and multiple organ failure.
- Nonspecific symptoms (like failure to thrive or feeding difficulties) may be the only symptoms of UTI in infants and elderly patients.

In uncomplicated UTI, patients respond rapidly to effective antibiotic therapy. Further evaluation, including urinalysis and culture, is recommended for patients with persistent symptoms or early recurrence to rule out pathogen resistant to initial therapy or to rule out other factors associated with complicated UTI.
Uncomplicated UTI can be reliably diagnosed on the basis of typical symptoms. Urinalysis and urine culture are not routinely needed; patients may be treated empirically.

Urinalysis and urine culture should be performed for patients if complicated UTI is suspected, and for patients with symptoms of pyelonephritis.

**Diagnostic Tests**

**Urinalysis** (dipstick or microscopic): Dipstick urinalysis performs best when urine culture yields growth $>10^5$ cfu/mL and dipstick shows positive leukocyte esterase and nitrite reactions (sensitivity 84%; specificity 98%). Sensitivity was significantly lower when the urine culture yielded growth $<10^5$ cfu/mL. The urine dipstick is not a reliable screen to rule out UTI. However, urinalysis has good specificity and may provide evidence to support a diagnosis of UTI. Most patients with UTI have pyuria (WBCs by microscopy or dipstick leukocyte esterase); WBC casts suggest pyelonephritis. Proteinuria and hematuria are also frequent findings. A positive dipstick nitrite reaction is typical for UTI caused by *E. coli* and other *Enterobacteriaceae*, but may be negative for other uropathogens, like *Enterococcus* species, *Pseudomonas* species and *S. saprophyticus*.

Algorithms using dipstick urinalysis have been proposed to reduce unnecessary antibiotic use while awaiting culture results. In patients at low risk for complicated UTI, three variables were used: dysuria, leukocytes greater than trace, and any positive nitrite reaction, including trace. Patients positive for two or three variables were treated without culture; culture was collected for patients with no or one positive variable and antibiotics withheld pending culture results. Using the algorithm, 80% of significant UTIs were detected; unnecessary antibiotic prescriptions were reduced by 23.5% and urine cultures by 59% compared with usual physician care.

**Gram stain:** Gram stain of an unconcentrated urine may be useful for detecting urine specimens that yield growth $>10^5$ cfu/mL, but are not reliable for detecting specimens that yield lower level, but significant growth. Because of the limited sensitivity for detecting significant cultures, and because of the labor intensity to perform, Gram staining is not recommended for urine specimens.

**Routine culture:** Quantitative culture is performed by inoculation of 1 microliter of urine onto SBA and selective (e.g., MacConkey or CNA) agar. The lower level of detection, therefore, is $10^1$ cfu/mL. The extent of workup (identification and susceptibility testing) depends on several factors, including: type of specimen (clean catch versus invasively collected), number of species isolated (pure culture versus mixed), pathogenic potential of isolate (typical uropathogen versus common contaminant) and quantity of growth. Laboratory workup is usually limited (descriptive ID only; no susceptibility testing) for cultures that yield mixed growth (3 or more species in comparable quantities), organisms with low uropathogenic potential (like *Lactobacillus* and diphtheroids), or isolates growing in quantities $<10^4$ cfu/mL.

**Culture for possible complicated UTI:** For symptomatic patients at risk for complicated UTI, bacteriuria at quantities $<10^{3-4}$ cfu/mL may predict...
significant UTI. For such patients, culture methods using a 10-microliter inoculum allow detection of growth at a lower detection limit of $10^2$ cfu/mL. The extent of workup follows similar guidelines used for routine cultures, except that full ID and appropriate susceptibility testing is performed when one or two uropathogens are isolated in quantities $>10^3$ cfu/mL (versus the $10^4$ cfu/mL cutoff used for routine cultures).

Urine culture may be normal in patients with renal or perinephric abscess if the infected tissue does not communicate with the collecting system. Drainage of such localized infections is performed for therapeutic reasons, as well as to collect material for culture, Gram stain and any other laboratory evaluation.

- Other Laboratory Testing:
  - Pregnancy testing may be appropriate for women presenting with otherwise uncomplicated UTI.
  - In patients with complicated UTI, blood cultures are recommended for patients with fever, hypotension, or other signs of sepsis. Other laboratory testing appropriate for the clinical presentation is recommended.

**Suggested Readings**


**TUBERCULOSIS, RENAL**

- **Definitions and Key Concepts**
  - Renal tuberculosis is a common form of extrapulmonary tuberculosis. The disease is caused by hematogenous seeding of the kidney during mycobacteremia that may occur during primary infection or late reactivation with miliary dissemination.

- **Who Should Be Suspected/Who Should Be Tested?**
  - The clinical manifestations of renal TB are variable; many patients show minimal symptoms and may be identified after workup for pyuria or microscopic hema-

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1Written by Michael J. Mitchell, MD.
turia, which are almost universally seen. Systemic symptoms are uncommon. Patients may complain of dysuria; gross hematuria may occur.

- Diagnosis should be suspected in a patient with a history or increased risk of mycobacterial disease, especially TB, and signs (e.g., microhematuria or pyuria) or symptoms (e.g., dysuria) of UTI. Routine urine culture is negative, although contaminated urine or coincidental UTI may confound the diagnosis.

**Diagnostic and Laboratory Findings**

- Patients with possible renal tuberculosis should be evaluated for pulmonary tuberculosis and infection at other extrapulmonary sites, as appropriate. Testing should include screening (e.g., TST), culture and imaging studies, as well as detailed physical examination and history.
- Mycobacteria are shed intermittently, so four to six first-morning samples should be submitted for mycobacterial culture. Mycobacterial culture of samples from other potentially infected sites is also recommended, as well as skin (or comparable) testing for TB. False-positive AFB smears may be seen due to nonpathogenic mycobacteria.
- Urinalysis typically shows WBCs; WBC casts are unusual. Some degree of hematuria is demonstrated in most patients.
- Renal function tests are usually normal; heavy proteinuria is uncommon.

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**EPIDIDYMITIS**

**Definition**

- Epididymitis is inflammation of the epididymis. The epididymis stores sperm cells received from the tubules of the rete testis, facilitates their maturation, and ultimately delivers them to the vas deferens.

**Who Should Be Suspected?**

- Epididymitis most commonly has an infectious etiology, presenting as either an acute condition (<6 weeks) or, more typically, chronic (≥6 weeks). The acute presentation is characterized by severe scrotal swelling and exquisite pain, often accompanied by high fever, rigors, and irritative voiding symptoms (frequency, urgency, and dysuria). The chronic presentation includes scrotal pain but usually lacks irritative voiding symptoms. Asymptomatic urethritis often accompanies epididymitis originating with sexually transmitted agents.
- Noninfectious epididymitis (precipitated by, e.g., trauma, autoimmune disease, or vasculitis) generally presents as a chronic condition, with less pain and swelling (less epididymal inflammation).
- The differential diagnosis of epididymitis should consider a range of other sources of scrotal pain and swelling, e.g., testicular torsion, Fournier gangrene (necrotizing fasciitis of the perineum with mixed aerobic/anaerobic bacteria), trauma/surgery, testicular cancer, inguinal hernia, Henoch-Schönlein purpura (IgA vasculitis), or epididymo-orchitis (e.g., post-mumps).
Laboratory Findings (Infectious Epididymitis)

- A urinalysis and urine culture should be performed on all patients suspected of urethritis. A urethral swab should be obtained in patients with urethral discharge and sent for culture and nucleic acid amplification testing for chlamydia and gonorrhea.
- In sexually active men under age 35, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most frequent causative agents. Combined infections by both agents are more frequently found than infections by *N. gonorrhoeae* alone.
- In men over age 35, *Escherichia coli*, other coliforms, and *Pseudomonas* species are more common. Less common pathogens include *Ureaplasma* species, *Mycobacterium tuberculosis*, and *Brucella* species, cytomegalovirus or *Cryptococcus* (patients with HIV infection).
- In boys before puberty, *E. coli* is a common cause.
- In children, epididymitis may be a response following infection by enterovirus, adenovirus, or *Mycoplasma pneumoniae*.

Suggested Readings


PROSTATITIS

Definition

- Prostatitis refers to histologic inflammation of the prostate gland, although the term is used loosely to describe several different conditions. The 1999 classification system of the National Institutes of Health Prostatitis Collaborative Network comprises four classes of prostatitis:
  - I. Acute bacterial prostatitis: Acute urogenital symptoms, with evidence of bacterial infection of the prostate. Route of entry is nearly always via the urethra or bladder through the prostatic duct, with intraprostatic reflux of urine and, sometimes, concomitant infection of the bladder or epididymis.
  - II. Chronic bacterial prostatitis: Chronic or recurrent urogenital symptoms with evidence of bacterial infection of the prostate. The route of entry is the same as for acute bacterial prostatitis.
  - IIIA. Chronic prostatitis/chronic pelvic pain syndrome, inflammatory: Chronic or recurrent urogenital symptoms with evidence of inflammation but not bacterial infection of the prostate.
  - IIIB. Chronic prostatitis/chronic pelvic pain syndrome, noninflammatory: Chronic or recurrent urogenital symptoms without evidence of inflammation or bacterial infection of the prostate.
  - IV. Asymptomatic inflammatory prostatitis: Absence of urogenital symptoms; evidence of inflammation of the prostate is found incidentally.
Who Should Be Suspected?

- Acute bacterial prostatitis (WHO class I) is manifested by a spiking fever, chills, malaise, myalgia, dysuria, irritative urinary symptoms (frequency, urgency, urge incontinence), pelvic or perineal pain, and cloudy urine. On exam, the prostate is often warm, firm, edematous, and exquisitely tender.

- Chronic bacterial prostatitis (WHO class II) is manifested (in a minority of patients) by symptoms of recurrent urinary tract infection (frequency, dysuria, urgency) with repeated isolation of the same organism from urine, perineal discomfort, and occasionally a low-grade fever. However, other patients may be asymptomatic, with persistent or recurrent bacteria in urine found incidentally during a workup for lower abdominal/perineal/genital pain or bladder irritation/obstruction.

- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is manifested by chronic pelvic pain for at least three of the preceding 6 months in the absence of other identifiable causes. Despite the name, it is uncertain that the symptoms can be traced to the prostate. WHO class IIIA CP/CPPS includes patients with inflammatory cells in expressed prostatic secretions, post–prostate massage urine, or seminal fluid. WHO class IIIB includes the balance of patients with chronic prostatitis or pelvic pain.

- Asymptomatic inflammatory prostatitis (WHO class IV) is usually diagnosed incidentally, during prostate biopsy or during a workup for infertility or cancer. The natural history of the syndrome is not well understood.

Laboratory Findings

- Acute bacterial prostatitis (WHO class I)
  - Blood: leukocytosis and an elevated serum prostate-specific antigen (PSA) support the diagnosis and should be followed by a digital rectal exam.
  - Urine: A Gram stain and culture should be obtained in all suspected cases. Bacteria causing acute prostatitis are easily recoverable from urine (prostate massage is contraindicated in suspected acute prostatitis, because it may induce sepsis). Culture usually reveals the causative organism (unless antibiotics were used recently).
  - Recovered organisms are generally those that induce UTI and urethritis: Escherichia coli, Klebsiella, Proteus, Pseudomonas, Enterobacter, Enterococcus, Serratia, and Staphylococcus aureus.
  - WBCs are found in the centrifuged urine sediment of the last portion of the voided urine specimen.

- Chronic bacterial prostatitis (WHO class II)
  - A presumptive diagnosis relies on chronic (>3 months) or recurrent urogenital symptoms, especially if bacteriuria is present. The standard diagnostic confirmation test is the Meares-Stamey four-glass test, which compares cultured bacterial colony counts in the first 5–10 mL (urethral) and midstream (bladder) urine specimens, a prostatic secretion (expressed by a 1-minute gentle prostate massage), and the first 5–10 mL of post–prostatic massage voided urine. If the bacteriuria baseline is
<10³/mL, chronic bacterial prostatitis is suspected if the leukocyte count in the prostatic secretion is >12 per high-power field and confirmed if >20 per high-power field (unless leukocytes were also present in the bladder urine specimen). A simpler “two-glass” method compares cultured bacterial colony counts collected from the midstream urine specimen (followed by the prostate massage) with the post-prostatic massage voided urine. This simpler method has a 100% positive and 96% negative predictive value.

- Cultures of the post-prostatic massage urine or expressed prostatic secretions are nearly always positive for bacteria. Repeated isolations of the same organism over time confirm the agent.
- Limitation: *Chlamydia trachomatis* will not grow in culture, so negative results by urine and prostatic secretion cultures should be followed by nucleic acid testing for this organism.

**Chronic prostatitis/chronic pelvic pain syndrome (WHO classes IIIA and IIIB)**

- A urinalysis should be performed on any patient suspected of prostatitis. The presence of hematuria should be followed up by urine cytology (for carcinoma in situ of the bladder), cystoscopy, and potentially upper tract imaging.
- A urine culture should also be performed to rule out a UTI. A recurrent UTI should be evaluated for chronic bacterial prostatitis (class II syndrome).
- Although bacterial infection has been implicated (especially in class IIIA), no agent has been consistently identified by culture or found by polymerase chain reaction (PCR) testing. Moreover, there is little correlation between histologic evidence of inflammation and the presence or absence of symptoms. The differential diagnosis is one of exclusion:
  - There is no low-grade fever (which can occur in the class II syndrome)
  - There is no prostatic hypertrophy, tenderness, or edema by rectal examination (as in the class II syndrome)
  - There are no systemic or neurologic symptoms (as in urethritis, urogenital cancer, urinary tract disease, urethral stricture, or neurologic disease affecting the bladder)

### Suggested Readings


INFERTILITY

OVERVIEW

Definition

- Infertility is defined as the inability to conceive after 12 or more months of regular intercourse without contraception.

- For a couple of normal fertility, the likelihood of pregnancy not occurring by 12 months is only 7%, which is close to the 5% figure often used as a threshold for a type 1 statistical error (here, falsely rejecting the null hypothesis of normal fertility). The likelihood of normal fertility decreases to 1% if pregnancy has not occurred after 3 years of intercourse without contraception.

- In a meta-analysis of 25 population surveys from 1991 to 2006, sampling 172,413 women, the 12-month prevalence rate of infertility ranged from 3.5 to 16.7% in more developed nations and 6.9 to 9.3% in developing nations.

- For those couples who have not been able to conceive despite 12 months of intercourse without contraception, a standard infertility evaluation is warranted for both partners. A two-part algorithm for the systematic assessment of the male partner is presented in Figure 7-2.

- Although there is an uncertain relationship between abnormalities found on tests of infertility versus actual causes of infertility, one population-based study reported the following results for all factors of infertility (male and female combined):
  - Male factors: 23%
  - Ovulatory disorders: 18%
  - Tubal damage: 14%
  - Endometriosis: 9%
  - Coital problems (e.g., impotence): 5%
  - Cervical factors: 3%
  - Unexplained: 28%

- Male factors of infertility can be divided into four general categories, of which the first three are amenable to laboratory diagnosis:
  - Testicular disease (primary defects, including Y chromosome deletions) (30–40%)
  - Posttesticular defects (disorders of sperm transport) (10–20%)
  - Secondary hypogonadism (1–2%)
  - Idiopathic (normal semen analysis, no other apparent cause) (40–50%)

- Female factors of infertility can also be divided into four general categories, of which the first category and hyperprolactinemia are amenable to laboratory diagnosis:
  - Ovulatory disorders (25%)
  - Tubal blockages or abnormalities (22%)
  - Endometriosis (15%)
  - Pelvic adhesions, hyperprolactinemia, and idiopathic (38%)
**Approach to diagnosis of male infertility**

1. Male infertility
   - History, physical examination, semen analysis

2. Reduced sperm count, often with abnormal morphology and <50 percent motility
3. Normal sperm count with abnormal morphology or decreased motility
4. Normal, with no abnormality in female

   - Repeat semen analysis

   - Normal, with no abnormality in female
     - Specialized tests of sperm function
     - Measure serum T, FSH, LH

   - Abnormal

   - ↓T  ↑FSH  ↑LH
     - Primary hypogonadism
     - Azoo- or severe oligozoospermia: Karyotype and Y chromosome microdeletions
     - Retrieve ejaculate or testicular sperm for ICSI

   - Normal T  ↑FSH  Normal LH
     - Germinal epithelium failure

   - Normal T  Normal FSH  Normal LH
     - Hypogonadotropic hypogonadism
     - Partial androgen resistance

   - ↓T  ↓FSH  ↓LH
     - ↑T  Normal FSH  ↑LH
     - See next figure

T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

**Figure 7–2** (From Swerdloff RS, Wang C. Evaluation of male infertility. In: Basow DS, ed. UpToDate. Waltham, MA: UpToDate, 2013.)
Approach to diagnosis of male infertility in patients with normal serum hormone concentrations

Male infertility, Normal serum T, FSH, LH

Semen analysis

Oligozoospermia, asthenozoospermia or teratozoospermia

Positive sperm antibodies

Sperm autoimmunity

Idiopathic

Y chromosome microdeletions

Varicoceles

ICSI

Azoospermia

Examine post-ejaculation urine

Sperm absent

Assess semen fructose

Sperm present

Retrograde ejaculation

Negative

Ultrasound seminal vesicles

Acquired obstruction of vas deferens at ejaculatory duct level

Dilated

Fine needle aspiration or open biopsy of testicles

Normal

Congenital absence of vas deferens

Obstruction of ductal system at epididymis

Normal

Abnormal

Obstruction of ductal system at epididymis

Germ cell arrest or hypospermatogenesis

Microsurgical aspiration of epididymal sperm and ICSI

If spermatids present in testis biopsy, ICSI with testicular sperm

T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

Figure 7–2  (Continued)

Suggested Readings


TESTICULAR DISEASE

Definition
- Testicular disease refers to primary testicular defects, including congenital and developmental disorders and acquired diseases. Testicular disease accounts for 30–40% of all causes of male infertility.

Who Should Be Suspected?
- For a couple experiencing infertility, the workup of the male begins with a history, physical examination, and standard semen analysis. Under certain circumstances, more specialized tests could help determine the cause. The presence of agglutination in the initial semen analysis suggests sperm autoimmunity, which should be confirmed by testing for antisperm autoantibodies. Azoospermia in the initial analysis, and the absence of sperm in concentrated postejaculation urine suggest a blockage, and assessing semen fructose is warranted.
- Chromosomal disorders affecting male fertility include Klinefelter syndrome (XXY and variants XXY/Y; XXXY), autosomal and X chromosome defects, and especially Y chromosome microdeletions and substitutions. Congenital disorders at the gene level include androgen receptor or postreceptor abnormalities, defective estrogen receptor or synthesis, inactivating receptor in the follicle-stimulating hormone (FSH) receptor gene, and myotonic dystrophy. Developmental disorders include cryptorchidism and varicoceles.
- Acquired diseases affecting male fertility include testicular cancer (with increasing frequency), debilitating illnesses (such as chronic renal insufficiency, cirrhosis, malnutrition, and sickle cell anemia), celiac disease, and a range of infections causing orchitis (mumps, echovirus, arbovirus, tuberculosis, leprosy, gonorrhea, and chlamydia).
- Other causes include certain drugs—alkylating agents (such as cyclophosphamide and chlorambucil), antiandrogens (such as flutamide, cyproterone, bicalutamide, spironolactone), ketoconazole, and cimetidine; ionizing radiation (doses as low as 0.015 Gy [15 rads] transiently suppressing spermatogenesis, doses above 6 Gy [600 rads] usually causing irreversible azoospermia and infertility); environmental toxins (such as lead, cadmium, mercury, and certain “endocrine disruptors” such as certain insecticides and fungicides); and smoking.

Laboratory Findings
- A positive test for antisperm autoantibodies suggests sperm autoimmunity, which could be clinically significant if >50% of the cells are coated and when such sperm fail to penetrate preovulatory human cervical mucus or demonstrate impaired fertilizing capacity.
- Low or nondetectable semen fructose is associated with ejaculatory duct obstruction or with congenital absence of the vas deferens.

Suggested Readings
**Chapter 7  ■  Genitourinary System Disorders**


**DISORDERS OF SPERM TRANSPORT**

- **Definition**
  - Disorders of sperm transport involve abnormalities at either of the critical sites along the male genital tract (the epididymis and the vas deferens) or ejaculatory dysfunction.

- **Who Should Be Suspected?**
  - For a couple experiencing infertility, in the workup of the male, the findings of azoospermia in the initial standard semen analysis, normal-sized testes, and normal serum levels of testosterone, FSH, and luteinizing hormone (LH) warrant checking for retrograde ejaculation with a postejaculatory urine specimen. If sperm are not present in the urine specimen, then the patient has obstructive azoospermia or impaired spermatogenesis. Assessing semen fructose is the next step in distinguishing an obstruction at the epididymis from an obstruction or absence of the vas deferens.

- **Laboratory Findings**
  - If semen fructose is present, epididymal obstruction is likely, but fine needle aspiration or open biopsy of the testis should be considered to confirm normal testicular histology. If the histologic analysis is abnormal, the conclusion is a germ cell arrest or hypospermatogenesis.
  - If semen fructose is absent, obstruction or absence of the vas deferens is likely, and ultrasound analysis of the seminal vesicles will allow one to distinguish an acquired obstruction (dilated seminal vesicles) from congenital absence (normal seminal vesicles).

Causes of acquired vas deferens obstructions include infection (gonorrhea, chlamydia, tuberculosis) and ligation (i.e., vasectomy). Only 2% of infertile men have congenital absence of the vas deferens, most stemming from mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, although other findings typical of CF are absent. Primary ciliary dyskinesias (affecting cilia function and transport) are a genetically diverse group of congenital defects that lead to abnormal transport of sperm within the vas deferens.

**Suggested Readings**


POSTVASECTOMY STATUS

Definition

Following a vasectomy, a series of semen analyses are performed for a defined period to determine the success or failure of the procedure. Azoospermia in a semen specimen is definitive evidence of a successful vasectomy.

Who Should Be Evaluated?

About four of five postvasectomy patients will be azoospermic after 3 months and 20 ejaculations. However, this period of time will be shorter if ejaculations are more frequent or if the patient is older.

In a low percentage of cases, postvasectomy patients will consistently evidence nonmotile sperm, possibly reflecting an undue delay between ejaculation and laboratory analysis. Repeat testing after 1 and 2 months may confirm azoospermia, but the continued presence of rare, nonmotile sperm at this point is probably clinically insignificant.

Laboratory Findings

A fresh specimen should be examined using direct phase-contrast microscopy (25–50 high-power fields). If sperm are not seen on the initial slide, a centrifuged specimen should be evaluated.

If motile sperm are present 3 months after the procedure and there have been more than 20 ejaculates, then the vasectomy is considered a failure.

Suggested Readings


OVULATORY DISORDERS

Definition

As a group, ovulatory disorders are characterized as either infrequent (oligo-ovulation) or absent (anovulation). In both disorders, the number of oocytes available for fertilization is reduced. Ovulatory disorders account for 25% of all causes of female infertility.

Who Should Be Suspected?

Candidates are women aged 16–40 years who report irregular or absent menses (amenorrhea) and irregular or absent molimina (breast tenderness, dysmenorrheal, bloating). Likely causes are pregnancy, oligoovulation (>36 days between menstrual cycles), or anovulation (>3–6 months without menses). Anovulation patients are classified by the WHO as:

- WHO1: hypogonadotrophic hypoestrogenic (15%)
- WHO2: normogonadotrophic normoestrogenic (80%)
- WHO3: hypergonadotrophic hypoestrogenic (5%)
Laboratory Findings

- WHO class 1: FSH is low or low-normal, and serum estradiol is low because of decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH.
- WHO class 2: FSH and estradiol are normal. The majority of anovulation patients belong to this group, with heterogeneous additional symptoms that include obesity, biochemical or clinical hyperandrogenism, and insulin resistance. Follow-up testing would include prolactin (covered in the next section), thyroid-stimulating hormone (TSH), and T₄. Thyroid abnormalities occur in up to 4% of patients with infertility. In patients with signs of hirsutism, testing should include testosterone and dehydroepiandrosterone (DHEA-sulfate). This group includes patients with polycystic ovary syndrome (PCOS), of whom 70% demonstrate elevated free testosterone. An additional test for PCOS is the 2-hour glucose tolerance test, which examines insulin and glucose levels following administration of a 75 g glucose bolus.
- WHO class 3: FSH is elevated. In patients with elevated FSH and a normal karyotype, the diagnosis should consider ovarian resistance (follicular form) or premature ovarian insufficiency (absence of ovarian follicles through early menopause). In patients under age 30 with elevated FSH, a karyotype analysis should be performed to check for Turner syndrome (XO) or XY females with gonadal dysgenesis.

Suggested Reading
Davis J, Segars J. Menstruation and menstrual disorders: anovulation. Glob Libr Women’s Med. (ISSN: 1756–2228); 2009; doi: 10.3843/GLOWM.10296

HYPERPROLACTINEMIA

Definition

Hyperprolactinemia is an abnormally high serum prolactin concentration in women of reproductive age. Excluding pregnancy, it accounts for 10–20% of cases of amenorrhea.

Who Should Be Suspected?

- In premenopausal women, hyperprolactinemia causes hypogonadism, manifested by infertility, oligomenorrhea, or amenorrhea, and less often by galactorrhea. The mechanism involves inhibition of LH, and possibly FSH as well, through inhibition of the release of GnRH. The symptoms of hyperprolactinemic hypogonadism in these patients directly correlate with serum prolactin concentration. In most laboratories, a serum prolactin concentration above 15–20 ng/mL (15–20 μg/L) is considered abnormally high for women of reproductive age.

Laboratory Findings (Premenopausal Women)

- 20–50 ng/mL (20–50 μg/L): Mild hyperprolactinemia, causing insufficient progesterone secretion and a short luteal phase of the menstrual cycle.
Infertility may be present despite no abnormality of the menstrual cycle. These patients account for about 20% of those evaluated for infertility.

- 50–100 ng/mL (50–100 μg/L): Moderate hyperprolactinemia, causing either amenorrhea or oligomenorrhea.
- 100 ng/mL (>100 μg/L): Associated with overt hypogonadism, subnormal estradiol secretion, and its consequences, including amenorrhea, hot flashes, and vaginal dryness.

**Suggested Reading**