Urinary Tract Infection

Urinary tract infection (UTI) is a term that is applied to a variety of clinical conditions ranging from the asymptomatic presence of bacteria in the urine to severe infection of the kidney with resultant sepsis. UTI is one of the more common medical problems. It is estimated that 150 million patients are diagnosed with a UTI yearly, resulting in at least $6 billion in healthcare expenditures. UTIs are at times difficult to diagnose; some cases respond to a short course of a specific antibiotic, while others require a longer course of a broad-spectrum antibiotic. Accurate diagnosis and treatment of a UTI is essential to limit its associated morbidity and mortality and avoid prolonged or unnecessary use of antibiotics. Advances in our understanding of the pathogenesis of UTI, the development of new diagnostic tests, and the introduction of new antimicrobial agents have allowed physicians to appropriately tailor specific treatment for each patient.

EPIDEMIOLOGY

Approximately 7 million cases of acute cystitis are diagnosed yearly in young women; this likely is an underestimate of the true incidence of UTI because at least 50% of all UTIs do not come to medical attention. The major risk factors for women 16–35 years of age are related to sexual intercourse and diaphragm use. Later in life, the incidence of UTI increases significantly for both males and females. For women between 36 and 65 years of age, gynecologic surgery and bladder prolapse appear to be important risk factors. In men of the same age group, prostatic hypertrophy/obstruction, catheterization, and surgery are relevant risk factors. For patients older than 65 years, the incidence of UTI continues to increase in both sexes. Incontinence and chronic use of urinary catheters are important risk factors in these patients. In those younger than 1 year and those older than 65 years, the morbidity and mortality of UTI are the greatest.

Based on data from the Urologic Diseases in North America Project, the overall lifetime prevalence of UTI was estimated to be 14,000 per 100,000 men and 53,000 per 100,000 women. Overall medical expenditures for the treatment of UTIs in the United States were estimated to be $1 billion for men and $2.5 billion for women. The increased costs in treatment of UTIs for women is primarily due to an increase in the trend toward using fluoroquinolones as a first-line therapy for UTI. UTIs occurred in 2.4–2.8% of children. In this patient population, UTIs resulted in more than 1.1 million physician visits annually, accounting for 0.7% of the doctor visits .

PATHOGENESIS

Bacterial Entry

Understanding of the mode of bacterial entry, host susceptibility factors, and bacterial pathogenic factors is essential to tailoring appropriate treatment for the diverse clinical manifestations of UTI. There are 4 possible modes of bacterial entry into the genitourinary tract. It is generally accepted that periurethral bacteria ascending into the urinary tract causes most UTI. Most cases of pyelonephritis are caused by the ascent of bacteria from the bladder, through the ureter and into the renal parenchyma. Consequently, the short nature of the female urethra combined with its close proximity to the vaginal vestibule and rectum likely predisposes women to more frequent UTIs than men.

Other modes of bacterial entry are uncommon causes of UTI. Hematogenous spread can occur in immunocompromised patients and in neonates. Staphylococcus aureus, Candida species, and Mycobacterium tuberculosis are common pathogens that travel through the blood to infect the urinary tract. Lymphatogenous spread through the rectal, colonic, and periuterine lymphatics has been postulated as a cause for UTI; however, currently there is little scientific support to suggest that dissemination of bacteria through lymphatic channels plays a role in the pathogenesis of UTI.

Host Defenses

Host factors have an essential role in the pathogenesis of UTI. Unobstructed urinary flow with the subsequent washout of ascending bacteria is essential in preventing UTI. In addition, the urine itself has specific characteristics (its osmolality, urea concentration, organic acid concentration, and pH) that inhibit bacterial growth and colonization. It also contains factors that inhibit bacterial adherence, such as Tamm-Horsfall glycoprotein.

The epithelium lining the urinary tract not only provides a physical barrier to infection but also have the capacity to recognize bacteria in order to innate host defenses. The urothelial cells express toll-like receptors (TLRs) that upon engagement by specific bacterial components lead to production of inflammatory mediators. In response to the presence of bacteria, cells lining the urinary tract secrete chemoattractants such as interleukin-8 to recruit neutrophils to the area and limit tissue invasion. Specific serum and urinary antibodies are produced by the kidney to enhance bacterial opsonization and phagocytosis and to inhibit bacterial adherence.

Many studies have demonstrated that there is selectivity in bacterial adherence to cells lining the urinary tract, and the degree of adherence correlates with colonization and infection. Women with recurrent UTIs have higher adherence of bacteria to their mucosal cells in vitro compared to women who never had an infection. The increased adherence may be due to having more binding sites for bacterial adhesins on their mucosal cells. Alternatively, these patients may not secrete soluble compounds, which normally compete for the same receptors that bind bacterial adhesins.

Other important host factors include the normal flora of the periurethral area or the prostate and the presence of vesicoureteral reflux. In women, the normal flora of the periurethral area composed of organisms such as lactobacillus provides a defense against the colonization of uropathogenic bacteria. Alterations in the periurethral environment (such as changes in the pH or estrogen levels or the use of antibiotics) can damage the periurethral flora, allowing uropathogens to colonize and subsequently to infect the urinary tract. In men, the prostate secretes fluid containing zinc, which has potent antimicrobial activity. Finally, in children, the presence of vesicoureteral reflux does not increase their susceptibility to UTI but does allow bacteria to be inoculated into the upper tract and the infection to progress.

Aging is associated with an increased susceptibility to UTI, in part because of the increased incidence of obstructive uropathy in men and alteration in the vaginal and periurethral flora from menopause in women. Other causes include soiling of the perineum from fecal incontinence, neuromuscular diseases, increased instrumentation, and bladder catheterization.

Bacterial Pathogenic Factors

Not all bacteria are capable of adhering to and infecting the urinary tract. Of the many strains of Escherichia coli, the uropathogens belong to a limited number of O, K, and H serogroups. They have increased adherence properties to uroepithelial cells, resistance to the bactericidal activity of human serum, production of hemolysin, and the increased expression of K capsular antigen. The ability of E. coli to adhere to epithelial cells is mediated by ligands located on the tips of the bacterial fimbriae (pili). The ligands bind to glycolipids or glycoprotein receptors on the surface membrane of uroepithelial cells. Once attachment to the uroepithelial cells occurs, other bacterial pathogenic factors become important. Most uropathogenic E. coli strains produce hemolysin, which initiates tissue invasion and makes iron available for the infecting pathogens. The presence of K antigen on the invading bacteria protects them from phagocytosis by neutrophils . These factors allow the infecting pathogens to escape the various host defenses.

Recently, it has been observed that many bacteria such as E. coli have the ability to invade into the host cells, acting as opportunistic intracellular pathogens. The intracellular bacteria mature into biofilms, creating podlike bulges on the urothelial surface. The pods contain bacteria encased in a polysaccharideric matrix surrounded by a protective shell of uroplakin. The ability of the uropathogenic bacteria to transiently invade, survive, and multiply within the host cells and to create biofilms on genitourinary tract tissues may provide a mechanism for the persistence and recurrence of UTIs.

CAUSATIVE PATHOGENS

Most UTIs are caused by a single bacterial species. At least 80% of the uncomplicated cystitis and pyelonephritis are due to *E. coli*, with most of pathogenic strains belonging to the O serogroups. Other less common uropathogens include Klebsiella, Proteus, and Enterobacter spp. and enterococci. In hospitalacquired UTIs, a wider variety of causative organisms is found, including Pseudomonas and Staphylococcus spp.; UTIs caused by S. aureus often result from hematogenous dissemination. Group B beta-hemolytic streptococci can cause UTIs in pregnant women. S. saprophyticus, once often thought of as urinary contaminants, can cause uncomplicated UTIs in young women. In children, the causative bacterial spectrum is slightly different from that of adults, with Klebsiella and Enterobacter spp. being more common causes of UTI. Anaerobic bacteria, lactobacilli, corynebacteria, streptococci (not including enterococci) and S. epidermidis are found in normal periurethral flora. They do not commonly cause UTIs in healthy individuals and are considered common urinary contaminants.

Diagnosis

The diagnosis of UTI relies on urinalysis and urine culture. Most often, the urine is obtained from a voided specimen. In children who are not toilet trained, a urine collection device, such as a bag, is placed over the genitalia, and the urine is cultured from the bagged specimen. These 2 methods of urine collection are easy to obtain, but potential contamination from the vagina and perirectal area may occur. There is a high false-positive rate, especially from bagged specimens. Suprapubic aspiration avoids potential contamination; however, due to its invasiveness, it is rarely used except in children and selected patients. Urine obtained from a urinary catheter is less invasive than a suprapubic aspiration and is less likely to be contaminated than that from a voided specimen. If a patient has an indwelling catheter, a urine specimen should be obtained from the collection port on the catheter.

Urinalysis

The urine can be immediately evaluated for leukocyte esterase, a compound produced by the breakdown of white blood cells (WBCs) in the urine. Urinary nitrite is produced by reduction of dietary nitrates by many gram-negative bacteria. Esterase and nitrite can be detected by a urine dipstick and are more reliable when the bacterial count is >100,000 colony-forming units (CFU) per milliliter. Microscopic examination of the urine for WBCs and bacteria is performed after centrifugation. When bacteria counts are >100,000 CFU/mL, bacteria can be detected microscopically. More than 3 WBCs per high-power field suggests a possible infection. The urinary nitrite test is highly specific but not sensitive, whereas the other 3 tests have a sensitivity and specificity approximately 80%. A combination of these tests may help to identify those patients in whom urine culture will be positive. Conversely, when esterase, nitrite, blood, and protein is absent in a urine, <2% of the urine samples will be positive by culture, providing a >98% negative predictive value and a sensitivity of 98% .

Urine Culture

The gold standard for identification of UTI is the quantitative culture of urine for specific bacteria. The urine should be collected in a sterile container and cultured immediately after collection. When this is not possible, the urine can be stored in the refrigerator for up to 24 hours. The sample is then diluted and spread on culture plates. Each bacterium will form a single colony on the plates. The number of colonies is counted and adjusted per milliliter of urine (CFU/mL). Traditionally, >100,000 CFU/mL is used to exclude contamination. However, studies have clearly demonstrated that clinically significant UTI can occur with <100,000 CFU/mL bacteria in the urine.

ANTIBIOTICS

Treatment with antimicrobial agents has minimized the morbidity and mortality associated with UTIs. The goal in treatment is to eradicate the infection by selecting the appropriate antibiotics that would target specific bacterial susceptibility. However, choosing the appropriate antimicrobial agents is often difficult. Many antibiotics are available, and the lowest effective dose and length of therapy are not well defined. Many conventions for the treatment of UTI are arbitrary. The general principles for selecting the appropriate antibiotics include consideration of the infecting pathogen (antibiotic susceptibility, single-organism versus poly-organism infection, pathogen versus normal flora, community versus hospital-acquired infection); the patient (allergies, underlying diseases, age, previous antibiotic therapy, other medications currently taken, outpatient versus inpatient status, pregnancy); and the site of infection (kidney versus bladder versus prostate). Because most antibiotics are cleared from the body by the liver or the kidney, certain antimicrobial agents need to be adjusted in the presence of liver or renal diseases.

Antibiotic Resistance

Drug resistance among uropathogens has increased steadily during the past several years and has much geographical variability. Among uropathogens particularly E. coli, resistance to ampicillin (18–54%), trimethoprim (9–27%), and sulfamethoxazole (16–49%) were high. Resistance to nitrofurantoin and fluoroquinolones were generally lower (<3%). However, with more extensive usage, resistance to these drugs is increasing. Even aminoglycosides which are considered to be effective, first-line choice for the treatment of complicated UTIs are not immune to the development of resistance. To limit the development of antibiotic resistance among uropathogens, judicial usage of antibiotics (duration and selection of the antibiotics) will be required. The present state of microbial resistance development is alarming . The use of antibiotics in different European countries mirrors the global increase in resistant strains . The presence of extended-spectrum β-lactamase (ESBL) producing bacteria showing resistance to most antibiotics, except for the carbapenem group, is steadily increasing in the population . Even more alarming are the recent reports from all continents about the emergence and increased prevalence of different carbapenemase producing organisms making them resistant even to the carbapenem group of antibiotics. Particularly troublesome is the increasing

resistance to broad-spectrum antibiotics, in particular to fluoroquinolones and cephalosporins, due to an overconsumption of these two groups and the parallel development of co-resistance to other antibiotics (collateral damage). This development is a threat to patients undergoing urological surgery in general and men subjected to prostate biopsy in particular. An urgent and strong grip on this threatening development is thus required. With only a few new antibiotics expected in the coming 5 to 10 years, prudent use of available antibiotics is the only option to delay the development of resistance and the urological community has a responsibility to participate in this combat. It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harbouring resistant microbes in individual patients.

CLINICAL PRESENTATION

KIDNEY INFECTION

Acute Pyelonephritis

Acute pyelonephritis is defined as inflammation of the kidney and renal pelvis, and its diagnosis is usually made clinically.

A. PRESENTATION AND FINDINGS

Patients with acute pyelonephritis present with chills, fever, and costovertebral angle tenderness. They often have accompanying lower-tract symptoms such as dysuria, frequency, and urgency. Sepsis may occur, with 20–30% of all systemic sepsis resulting from a urine infection. Urinalysis commonly demonstrates the presence of WBCs and red blood cells in the urine. Leukocytosis, increased erythrocyte sedimentation, and elevated levels of C-reactive protein are commonly seen on blood analysis. Bacteria are cultured from the urine when the culture is obtained before antibiotic treatment is instituted. E. coli is the most common causative organism, accounting for 80% of the cases. Klebsiella, Proteus, Enterobacter,

Pseudomonas, Serratia, and Citrobacter spp. account for the remaining cases. Of the gram-positive bacteria, Streptococcus faecalis and S. aureus can be important causes of pyelonephritis. In reproductive-age women, sexual activity, patient and family history of UTI are associated with an increased risk of developing pyelonephritis. Diabetes and urinary incontinence also independently increase this risk.

B. RADIOGRAPHIC IMAGING

Contrast-enhanced computed tomography (CT) scans can accurately demonstrate findings, confirming the diagnosis of pyelonephritis. Acute bacterial infection causes constriction of peripheral arterioles and reduces perfusion of the affected renal segments. Perfusion defects, which can be segmental, multifocal, or diffuse, are seen as areas of reduced signal density. Renal enlargement, attenuated parenchyma, and a compressed collecting system are other characteristic findings on CT scan. However, CT scan is not necessary unless the diagnosis is unclear or the patient is not responding to therapy. In patients with acute pyelonephritis, renal ultrasonography is important to rule out concurrent urinary tract obstruction but cannot reliably detect inflammation or infection of the kidney.

C. MANAGEMENT

The management of acute pyelonephritis depends on the severity of the infection. In patients who have toxicity because of associated septicemia, hospitalization is warranted. Approximately 10–30% of all adult patients with acute pyelonephritis require hospitalization. In mild and moderate cases of acute uncomplicated pyelonephritis oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% . If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days. However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the world, thus restricting the empirical use of fluoroquinolones, and fluoroquinolones are contraindicated during pregnancy. A third-generation oral cephalosporin, such as cefpodoxime proxetil or ceftibuten, could be an alternative. However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin. As a result of increasing *E. coli* resistance rates >10%, cotrimoxazole is not suitable for empirical

therapy in most areas, but it can be used after sensitivity has been confirmed through susceptibility testing. Co-amoxiclav is not recommended as a drug of first choice for empirical oral therapy of acute pyelonephritis. It is recommended when susceptibility testing shows a susceptible Gram-positive organism. In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli* (> 10%), initial empirical therapy with an aminoglycoside or carbapenem has to be considered until susceptibility testing demonstrates that oral drugs can also be used.

Fever from acute pyelonephritis may persist for several days despite appropriate therapy. Parenteral therapy should be maintained until the patient defeversces. If bacteremia is present, parenteral therapy should be continued for an additional 7–10 days and then the patient should be switched to oral treatment for 10–14 days. Therapy should continue for 10–14 days.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a rare necrotizing infection characterized by the presence of gas within the renal parenchyma or perinephric tissue. About 80–90% of patients with emphysematous pyelonephritis have diabetes; the rest of the cases are associated with urinary tract obstruction from calculi or papillary necrosis. Patients with emphysematous pyelonephritis present with fever, flank pain, and vomiting that fails initial management with parenteral antibiotics. Pneumaturia may be present. Bacteria most frequently cultured from the urine include E. coli, Klebsiella pneumoniae, and Enterobacter cloacae.

B. RADIOGRAPHIC IMAGING

The diagnosis of emphysematous pyelonephritis is made after radiographic examination. Gas overlying the affected kidney may be seen on a plain abdominal radiograph (KUB). CT scan is much more sensitive in detecting the presence of gas in the renal parenchyma than renal ultrasonography.

C. MANAGEMENT

In the management of emphysematous pyelonephritis, prompt control of blood glucose and relief of urinary obstruction is essential, in addition to fluid resuscitation and parenteral

antibiotics. The mortality rate is 11–54%. Poor prognostic factors include high serum creatinine level, low platelet count, and the presence of renal/perirenal fluid in asso- ciation with a bubbly/loculated gas pattern or gas in the collecting system. In combination with medical treatment, percutaneous drainage appears to be helpful in accelerating resolution of the infection and minimizing the morbidity and mortality of the infection. Nephrectomy may be required if there is no function in the affected kidney. About 3–4 weeks of parenteral antibiotic therapy is usually required.

Chronic Pyelonephritis

Chronic pyelonephritis results from repeated renal infection, which leads to scarring, atrophy of the kidney, and subsequent renal insufficiency. The diagnosis is made by radiologic or pathologic examination rather than from clinical presentation.

A. PRESENTATION AND FINDINGS

Many individuals with chronic pyelonephritis have no symptoms, but they may have a history of frequent UTIs. In children, there is a strong correlation between renal scarring and recurrent UTIs. The developing kidney appears to be very susceptible to damage, and this susceptibility appears to be age dependent. Renal scarring induced by UTIs is rarely seen in adult kidneys. Because patients with chronic pyelonephritis often are asymptomatic, the diagnosis is made incidentally when radiologic investigation is initiated to evaluate for the complications associated with renal insufficiency, such as hypertension, visual impairments, headaches, fatigue, and polyuria. In these patients, urinalysis may show leukocytes or proteinuria but is likely to be normal. Serum creatinine levels reflect the severity of the renal impairment. Urine cultures are only positive when there is an active infection.

B. RADIOGRAPHIC IMAGING

Intravenous pyelogram or CT scan can readily demonstrate a small and atrophic kidney on the affected side. Focal coarse renal scarring with clubbing of the underlying calyx is characteristic. Ultrasonography similarly can demonstrate these findings.

C. MANAGEMENT

The management of chronic pyelonephritis is somewhat limited because renal damage incurred by chronic pyelonephritis is not reversible. Eliminating recurrent UTIs and identifying and correcting any underlying anatomic or functional urinary problems such as obstruction or urolithiasis can prevent further renal damage. In children, evaluation for vesicoureteral reflux with a voiding cystourethrogram is important to eliminate a risk factor for recurrent pyelonephritis and renal scarring. Long-term use of continuous prophylactic antibiotic therapy may be required to limit recurrent UTIs and renal scarring. Rarely, removal of the affected kidney may be necessary due to hypertension or having a large stone burden in a nonfunctioning kidney.

Renal Abscesses

Renal abscesses result from a severe infection that leads to liquefaction of renal tissue; this area is subsequently sequestered, forming an abscess. They can rupture out into the perinephric space, forming perinephric abscesses. When the abscesses extend beyond the Gerota's fascia, paranephric abscesses develop. Historically, most renal/perinephric abscesses result from hematogenous spread of staphylococci, in particular from infected skin lesions. Patients with diabetes, those undergoing hemodialysis, or intravenous drug abusers were at high risk for developing renal abscesses. With the development of effective antibiotics and better management of diseases such as diabetes and renal failure, renal/perinephric abscesses due to gram-positive bacteria are less prevalent; those caused by E. coli or Proteus species are becoming more common. Abscesses that form in the renal cortex are likely to arise from hematogenous spread, whereas those in the corticomedullary junction are caused from gram-negative bacteria in conjunction with some other underlying urinary tract abnormalities, such as stones or obstruction.

A. PRESENTATION AND FINDINGS

The most common presenting symptoms in patients with renal/perinephric abscesses include fever, flank or abdominal pain, chills, and dysuria. Many of the symptoms have lasted for more than 2 weeks. A flank mass may be palpated in some patients. Urinalysis usually demonstrates WBCs; however, it may be normal in approximately 25% of the cases. Urine cultures only

identify the causative organisms in about one-thirds of cases and blood cultures in only about half of cases.

B. RADIOGRAPHIC IMAGING

Renal abscesses can be accurately detected using ultrasonography or CT scans. There is a wide range of ultrasonographic findings ranging from an anechoic mass within or displacing the kidney to an echogenic fluid collection that tends to blend with the normally echogenic fat within Gerota's fascia. With high sensitivity, CT scans can demonstrate an enlarged kidney with focal areas of hypoattenuation early on during the course of the infection. Once the inflammatory wall forms around the fluid collection, the abscess appears as a mass with a rim of contrast enhancement, the "ring" sign. CT scans may also demonstrate thickening of Gerota's fascia, stranding of the perinephric fat, or obliteration of the surrounding soft-tissue planes.

C. MANAGEMENT

The appropriate management of renal abscess first must include appropriate antibiotic therapy. Empiric therapy with broad-spectrum antibiotics is usually recommended. If the patient does not respond within 48 hours of treatment, percutaneous drainage under CT or ultrasound guidance is indicated. The drained fluid should be cultured for the causative organisms. If the abscess still does not resolve, then open surgical drainage or nephrectomy may be necessary. Follow-up imaging is needed to confirm resolution of the abscesses. These patients will also require evaluation for underlying urinary tract abnormalities such as stone or obstruction after the infection has resolved.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a rare form of chronic bacterial infection of the kidney. The affected kidney is almost always hydronephrotic and obstructed. In most cases,

XGP occurs unilaterally. Severe inflammation and necrosis obliterate the kidney parenchyma. Characteristically, foamy lipidladen histiocytes (xanthoma cells) are present and may be mistaken for renal clear cell carcinoma.

A. PRESENTATION AND FINDINGS

Patients with XGP commonly present with flank pain, fever, chills, and persistent bacteriuria. A history of urolithiasis is present in about 35% of the patients. On physical examination, a flank mass can often be palpated. Urinalysis commonly demonstrates WBCs and protein. Serum blood analysis reveals anemia and may show hepatic dysfunction in approximately 50% of the patients. Because XGP primarily occurs unilaterally, azotemia or renal failure is not often seen. E. coli or Proteus species are commonly cultured from the urine. Approximately 10% of the patients with XGP have mixed organisms or anaerobic bacteria identified in their urine. Culture of the affected renal tissue can reliably identify the causative organism.

B. RADIOGRAPHIC IMAGING

CT scan is the most reliable method in imaging patients suspected of having XGP. It usually demonstrates a large heterogeneous, reniform mass. The renal parenchyma is often marked with multiple water-density lesions, representing dilated calyces or abscesses. On contrast-enhanced images, these lesions will have a prominent blush peripherally, while the central areas, which are filled with pus and debris, do not enhance. An area of central calcification surrounded by a contracted pelvis may also be seen. The inflammatory process may be seen extending to the perinephric fat, the retroperitoneum, and adjacent organs such as the psoas muscle, spleen, colon, or the great vessels. Because of the association of urolithiasis and XGP, renal calculi may be seen . Renal ultrasonography can also be used in performing imaging on patients with XGP. It usually reveals an enlarged kidney with a large central echogenic area and anechoic parenchyma. It is not uncommon for XGP to be misdiagnosed as a renal tumor because of their similar appearances on radiologic imaging.

C. MANAGEMENT

The management of XGP is dependent on accurate diagnosis. In some cases, XGP is misdiagnosed as a renal tumor. A nephrectomy is performed and a diagnosis is made pathologically. In those in whom a diagnosis of XGP is suspected, kidney-sparing surgery such

as a partial nephrectomy is indicated. However, when the infection is extensive, a nephrectomy with excision of all involved tissue is warranted.

Pyonephrosis

Pyonephrosis refers to bacterial infection of a hydronephrotic, obstructed kidney, which leads to suppurative destruction of the renal parenchyma and potential loss of renal function. Because of the extent of the infection and the presence of urinary obstruction, sepsis may rapidly ensue, requiring rapid diagnosis and management.

A. PRESENTATION AND FINDINGS

Patients with pyonephrosis are usually very ill, with high fever, chills, and flank pain. Lower-tract symptoms are not usually present. Bacteriuria and pyuria may not be present when there is complete obstruction of the affected kidney.

B. RADIOGRAPHIC IMAGING

Imaging with renal ultrasonography can be performed to rapidly diagnose pyonephrosis. Ultrasonographic findings include persistent echoes in the inferior portion of the collecting system, fluid-debris level with dependent echoes that shift with positional changes, strong echoes with acoustic shadowing from air in the collecting system, and weak echoes throughout a dilated collecting system. Renal or ureteral calculi may also be identified on ultrasonography.

C. MANAGEMENT

Management of pyonephrosis includes immediate institution of antibiotic therapy and drainage of the infected collecting system. Broad-spectrum antimicrobials are indicated to prevent sepsis while the causative organism is being identified; antibiotics should be started before manipulation of the urinary tract. Performing drainage of the obstruction through the lower urinary tract (such as using a ureteral stent) should be reserved for patients who are not septic. Extensive manipulation may rapidly induce sepsis and toxemia. In the ill patient, drainage of the collecting system with a percutaneous nephrostomy tube is preferable. Once the infection is

treated, additional imaging evaluation is required to identify the cause of the urinary obstruction, such as urolithiasis or ureteropelvic junction obstruction.

BLADDER INFECTION

Acute Cystitis

Acute cystitis refers to urinary infection of the lower urinary tract, principally the bladder. Acute cystitis more commonly affects women than men. The primary mode of infection is ascending from the peri-urethral/vaginal and fecal flora. The diagnosis is made clinically.

A. PRESENTATION AND FINDINGS

Patients with acute cystitis present with irritative voiding symptoms such as dysuria, frequency, and urgency. Low back and suprapubic pain, hematuria, and cloudy/foul-smelling urine are also common symptoms. Fever and systemic symptoms are rare. Typically, urinalysis demonstrates WBCs in the urine, and hematuria may be present. Urine culture is required to confirm the diagnosis and identify the causative organism. However, when the clinical picture and urinalysis are highly suggestive of the diagnosis of acute cystitis, urine culture may not be needed. E. coli causes most of the acute cystitis. Other gram-negative (Klebsiella and Proteus spp.) and gram-positive (S. saprophyticus and enterococci) bacteria are uncommon pathogens. Diabetes and lifetime history of UTI are risk factors for acute cystitis.

B. RADIOGRAPHIC IMAGING

In uncomplicated infection of the bladder, radiologic evaluation is not necessary.

C. MANAGEMENT

Management for acute cystitis consists of a short course of oral antibiotics. Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo. The choice of antibiotic therapy should be guided by:

• spectrum and susceptibility patterns of the aetiological uropathogens;

• efficacy for the particular indication in clinical studies;

- tolerability and adverse reactions;
- adverse ecological effects;
- cost;
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available. These regimens are recommended for women, but not for men. Most ESBL-producing *E. coli* are still susceptible to fosfomycin. However, in Spain a parallel increase in community use of fosfomycin and resistance to fosfomycin in ESBL-producing *E. coli* has been observed. Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20%. Despite still lower resistance rates in some areas, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection of resistance. Aminopenicillins are no more suitable for empirical therapy because of the worldwide high *E. coli* resistance. Aminopenicillins in combination with a betalactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are in general not so effective as short-term therapy and are not recommended for empirical therapy because of ecological collateral damage, but can be used in selected cases.

Recurrent Cystitis/UTI

A. PRESENTATION AND FINDINGS

Recurrent cystitis/UTI is caused either by bacterial persistence or reinfection with another organism. Identification of the cause of the recurrent infection is important, because the management of bacterial persistence and reinfection are distinct. If bacterial persistence is the

cause of recurrent UTI, the removal of the infected source is often curative, whereas preventative therapy is effective in treating reinfection.

B. RADIOGRAPHIC IMAGING

When bacterial persistence is the suspected cause, radiologic imaging is indicated. Ultrasonography can be obtained to provide a screening evaluation of the genitourinary tract. More detailed assessment with intravenous pyelogram, cystoscopy, and CT scans may occasionally be necessary. In patients who have frequent, recurrent UTI, bacterial localization studies and more extensive radiologic evaluation (such as retrograde pyelograms) is warranted. When bacterial reinfection is the suspected cause of recurrent cystitis, the patient should be carefully evaluated for evidence of vesicovaginal or vesicoenteric fistula. Otherwise, radiologic examination is often not necessary in these patients.

C. MANAGEMENT

Management of recurrent cystitis, again, depends on its cause. Surgical removal of the infected source (such as urinary calculi) is needed to treat bacterial persistence. Similarly, fistulas need to be repaired surgically to prevent bacterial reinfection. In most cases of bacterial reinfection, medical management with prophylactic antibiotics is indicated. Low-dose continuous prophylactic antibiotic has been shown to reduce the recurrences of UTI by 95% compared to placebo or historical controls. Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs include e.g. nitrofurantoin (macrocrystal) 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every 10 days, and during pregnancy e.g. cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily. In general, the choice of antibiotics should be based upon the identification and susceptibility pattern of the organism causing the UTI, the patient's history of drug allergies and the ecological collateral effects including bacterial selection of resistance by the chosen antimicrobial. Using these principles, several issues need to be considered:

- Ecological collateral effects mean that oral fluoroquinolones and cephalosporins are no longer recommended routinely, except in specific clinical situations.
- The worldwide increase of *E. coli* resistance against trimethoprim casts doubts on trimethoprim with or without a sulphonamide to be an effective prophylactic agent still.

• There are recent warnings by governmental agencies for the long-term prophylactic use of nitrofurantoin because of the rare but severe pulmonary and hepatic adverse effects.

PROSTATE INFECTION

Acute Bacterial Prostatitis

Acute bacterial prostatitis refers to inflammation of the prostate associated with a UTI. It is thought that infection results from ascending urethral infection or reflux of infected urine from the bladder into the prostatic ducts. In response to bacterial invasion, leukocytes (polymorphonuclear leukocytes, lymphocytes, plasma cells, and macrophages) are seen within and surrounding the acini of the prostate. Edema and hyperemia of the prostatic stroma frequently develop. With prolonged infection, variable degree of necrosis and abscess formation can occur.

A. PRESENTATION AND FINDINGS

Acute bacterial prostatitis is uncommon in prepubertal boys but frequent affects adult men. It is the most common urologic diagnosis in men younger than 50 years. Patients with acute bacterial prostatitis usually present with an abrupt onset of constitutional (fever, chills, malaise, arthralgia, myalgia, lower back/rectal/perineal pain) and urinary symptoms (frequency, urgency, dysuria). They may also present with urinary retention due to swelling of the prostate. Digital rectal examination reveals tender, enlarged glands that are irregular and warm. Urinalysis usually demonstrates WBCs and occasionally hematuria. Serum blood analysis typically demonstrates leukocytosis. Prostate-specific antigen levels are often elevated as well as CRP. The diagnosis of prostatitis is made with microscopic examination and culture of the prostatic expressate and culture of urine obtained before and after prostate massage. In patients with acute prostatitis, fluid from the prostate massage often contains leukocytes with fat-laden macrophages. However, at the onset of acute prostatitis, prostatic massage is usually not suggested because the prostate is quite tender and the massage may lead to bacteremia.

Similarly, urethral catheterization should be avoided. Culture of urine and prostate expressate usually identifies a single organism, but occasionally, polymicrobial infection may occur. E. coli is the most common causative organism in patients with acute prostatitis. Other gram-negative bacteria (Proteus, Klebsiella, Enterobacter, Pseudomonas, and Serratia spp.) and enterococci are less frequent pathogens. Anaerobic and other gram-positive bacteria are rarely a cause of acute prostatitis.

B. RADIOLOGIC IMAGING

Radiologic imaging is rarely indicated in patients with acute prostatitis. Bladder ultrasonography may be useful in determining the amount of residual urine. Transrectal ultrasonography is only indicated in patients who do not respond to conventional therapy.

C. MANAGEMENT

Treatment with antibiotics is essential in the management of acute prostatitis. Empiric therapy directed against gram-negative bacteria and enterococci should be instituted immediately, while awaiting the culture results. Fluoroquinolones have high drug penetration into prostatic tissue and are recommended for 4–6 weeks. The long duration of antibiotic treatment is to allow complete sterilization of the prostatic tissue to prevent complications such as chronic prostatitis and abscess formation. Patients with urinary retention secondary to acute prostatitis should be managed with a suprapubic catheter because transurethral catheterization or instrumentation is contraindicated.

Chronic Bacterial Prostatitis

In contrast to the acute form, chronic bacterial prostatitis has a more insidious onset, characterized by relapsing, recurrent UTI caused by the persistence of pathogen in the prostatic fluid despite antibiotic therapy.

A. PRESENTATION AND FINDINGS

Most patients with chronic bacterial prostatitis typically present with dysuria, urgency, frequency, nocturia, and low back/perineal pain. These patients usually are afebrile and not

uncommonly have a history of recurrent or relapsing UTI, urethritis, or epididymitis caused by the same organism. Others are asymptomatic, but the diagnosis is made after investigation for bacteriuria. In patients with chronic bacterial prostatitis, digital rectal examination of the prostate is often normal; occasionally, tenderness, firmness, or prostatic calculi may be found on examination. Urinalysis demonstrates a variable degree of WBCs and bacteria in the urine, depending on the extent of the disease. Serum blood analysis normally does not show any evidence of leukocytosis. Prostate-specific antigen levels may be elevated. Diagnosis is made after identification of bacteria from prostate expressate or urine specimen after a prostatic massage. The causative organisms are similar to those of acute bacterial prostatitis.

B. RADIOLOGIC IMAGING

Radiologic imaging is rarely indicated in patients with chronic prostatitis. Transrectal ultrasonography is only indicated if a prostatic abscess is suspected.

C. MANAGEMENT

Antibiotic therapy is similar to that for acute bacterial prostatitis. In patients with chronic bacterial prostatitis, the duration of antibiotic therapy may be 3–4 months. Using fluoroquinolones, some patients may respond after 4–6 weeks of treatment. The addition of an alpha blocker to antibiotic therapy has been shown to reduce symptom recurrences. Despite maximal therapy, cure is not often achieved due to poor penetration of antibiotic into prostatic tissue and relative isolation of the bacterial foci within the prostate.

Prostate Abscess

Most cases of prostatic abscess result from complications of acute bacterial prostatitis that were inadequately or inappropriately treated. Prostatic abscesses are often seen in patients with diabetes; those receiving chronic dialysis; or patients who are immunocompromised, undergoing urethral instrumentation, or who have chronic indwelling catheters.

A. PRESENTATION AND FINDINGS

Patients with prostatic abscess present with similar symptoms to those with acute bacterial prostatitis. Typically, these patients were treated for acute bacterial prostatitis previously and had a good initial response to treatment with antibiotics. However, their symptoms recurred during treatment, suggesting development of prostatic abscesses. On digital rectal examination, the prostate is usually tender and swollen. Fluctuance is only seen in 16% of patients with prostatic abscess.

B. RADIOLOGIC IMAGING

Imaging with transrectal ultrasonography or pelvic CT scan is crucial for diagnosis and treatment.

C. MANAGEMENT

Antibiotic therapy in conjunction with drainage of the abscess is required. Transrectal ultrasonography or CT scan can be used to direct transrectal drainage of the abscess. Transurethral resection and drainage may be required if transrectal drainage is inadequate. When properly diagnosed and treated, most cases of prostatic abscess resolve without significant sequelae.

URETHRITIS

Types of Urethritis

Infection/inflammation of the urethra can be categorized into those types caused by Neisseria gonorrhoeae and by other organisms (Chlamydia trachomatis, Ureaplasma ure- alyticum, Trichomonas vaginalis, and herpes simplex virus) (Dixon, Pearson, and Clutterbuck, 2002). Most cases are acquired during sexual intercourse.

A. PRESENTATION AND FINDINGS

Patients with urethritis may present with urethral discharge and dysuria. The amount of discharge may vary significantly, from profuse to scant amounts. Obstructive voiding

symptoms are primarily present in patients with recurrent infection, in whom urethral strictures subsequently develop. It is important to note that approximately 40% of patients with gonococcal urethritis are asymptomatic. The diagnosis is made from examination and culture of the urethra. It is important to obtain the specimen from within the urethra, rather than from just the discharge. Approximately 30% of men infected with N. gonorrhoeae will have concomitant infection with C. trachomatis.

B. RADIOLOGIC IMAGING

Retrograde urethrogram is only indicated in patients with recurrent infection and obstructive voiding symptoms. Most patients with uncomplicated urethritis do not require any radiologic imaging.

C. MANAGEMENT

Pathogen-directed antibiotic therapy is required. In patients with gonococcal urethritis, ceftriaxone (250 mg intramuscularly) or fluoroquinolones (ciprofloxacin 250 mg) or norfloxacin (800 mg) may be used. For patients with nongonococcal urethritis, treatment is with tetracycline or erythromycin (500 mg 4 times daily) or doxycycline (100 mg twice daily) for 7–14 days. However, the most essential component of treatment is prevention. Sexual partners of the affected patients should be treated, and protective sexual practices (such as using condoms) are recommended.

EPIDIDYMITIS

Causes of Epididymitis

Infection and inflammation of the epididymis most often result from an ascending infection from the lower urinary tract. Most cases of epididymitis in men younger than 35 years are due to sexually transmitted organisms (N. gonorrhoeae and C. trachomatis); those in children and older men are due to urinary pathogens such as E. coli. The infection in the epididymis may spread to involve the testis.

A. PRESENTATION AND FINDINGS

Patients with epididymitis present with severe scrotal pain that may radiate to the groin or flank. Scrotal enlargement due to the inflammation of the epididymis/testis or a reactive hydrocele may develop rapidly. Other symptoms of urethritis, cystitis, or prostatitis may be present before or concurrent with the onset of scrotal pain. On physical examination, an enlarged and red scrotum is present, and it is often difficult to distinguish the epididymis from the testis during the acute infection. A thickened spermatic cord can occasionally be palpated. Urinalysis typically demonstrates WBCs and bacteria in the urine or urethral discharge. Serum blood analysis often reveals leukocytosis.

B. RADIOLOGIC IMAGING

Frequently, it is difficult to distinguish epididymitis from acute testicular torsion based on the history and physical examination alone. Scrotal Doppler ultrasonography or radionuclide scanning can be used to confirm the diagnosis. The presence of blood flow in the testis on Doppler ultrasonography or uptake of the tracers into the center of the testis on radionuclide scanning rules out torsion. On scrotal ultrasonography, patients with epididymitis commonly have an enlarged epididymis with increased blood flow. A reactive hydrocele or testicular involvement may also be seen.

C. MANAGEMENT

Oral antibiotic treatment is directed against specific causative organisms, as mentioned in the previous sections on urethritis and UTI. In addition, bed rest, scrotal elevation, and the use of nonsteroidal anti-inflammatory agents are helpful in reducing the duration of the symptoms. In patients with epididymitis caused by sexually transmitted organisms, treatment of their sexual partners is recommended to prevent reinfection. For patients with sepsis or severe infection, hospitalization and parenteral antibiotic therapy may be needed. Open drainage is indicated in cases in which an abscess develops. Occasionally, patients with chronic, relapsing epididymitis and scrotal pain may require epididymectomy for relief of their symptoms.

SPECIAL CIRCUMSTANCES

UTI Related to Pregnancy

With pregnancy, there are anatomic and physiologic changes to the urinary tract due to compression by the gravid uterus and alterations in the hormonal milieu. Renal length increases approximately by 1 cm during normal pregnancy as a result of increased vascular and interstitial volume. The glomerular filtration rate increases by 30–50%, most likely secondary to the increase in cardiac output. Typically, there is significant ureteral dilation with resultant urinary stasis during the second and third trimesters of gestation. This hydroureter is attributed to the smooth muscle–relaxing effects of progesterone and the mechanical compression of the ureters by the uterus at the level of the pelvic rim. The bladder is also affected, both physically and physiologically. The enlarged uterus displaces the bladder superiorly and anteriorly. The bladder becomes hyperemic, and its capacity is increased, most likely due to the effects of progesterone.

Because of these changes in the urinary tract during normal pregnancy, bacteriuria is a clinically relevant finding in pregnant women. It is estimated that the prevalence of bacteriuria is 4–6%, which is not significantly different from that in nonpregnant women of comparable age. Interestingly, approximately 30% of those who have bacteriuria on screening evaluation later have pyelonephritis, compared to only 1–2% in those who do not have bacteriuria. Treatment of bacteriuria decreases the incidence of pyelonephritis during pregnancy to approximately 3% .

Overall, the incidence of acute bacterial pyelonephritis is 1–4% in pregnant women. About 60–70% of the episodes of pyelonephritis occur during the second and third trimesters of pregnancy, when urinary stasis is the greatest. In 10–20%, recurrent episodes of pyelonephritis develop before delivery. Significant maternal risk factors include diabetes and history of UTI. When left untreated, pyelonephritis during pregnancy is associated with a high rate of infant prematurity and its associated perinatal mortality. Consequently, it is recommended that women be screened for bacteriuria during pregnancy to prevent the development of pyelonephritis. For asymptomatic individuals, significant bacteriuria is defined as 2 voided urine cultures with >105 CFU/mL of a single organism. For symptomatic pregnant women,

>103 CFU/ mL is considered to be significant. Pregnant women who are found to have bacteriuria should be treated with penicillins, oral cephalosporins, or fosfomycin trometamol. However, amoxicillin is not recommended because of the rate of bacterial resistance. A 3-day course is suggested, although single-dose therapy may be effective in some patients. Repeat urine culture to document eradication of bacteriuria is necessary in all patients. Patients with acute bacterial pyelonephritis should be treated with parenteral cephalosporins, penicillins with beta-lactamase inhibitors, or monolactams. Periodic surveillance urine culture is recommended because many of these women will have recurrent episodes of pyelonephritis.

TUBERCULOSIS

Tubercle bacilli may invade one or more (or even all) of the organs of the genitourinary tract and cause a chronic granulomatous infection that shows the same characteristics as tuberculosis in other organs. Urinary tuberculosis is a disease of young adults (60% of patients are between the ages of 20 and 40) and is a little more common in males than in females.

Etiology

The infecting organism is Mycobacterium tuberculosis, which reaches the genitourinary organs by the hematogenous route from the lungs. The primary site is often not symptomatic or apparent.

The kidney and possibly the prostate are the primary sites of tuberculous infection in the genitourinary tract. All other genitourinary organs become involved by either ascent (prostate to bladder) or descent (kidney to bladder, prostate to epididymis). The testis may become involved by direct extension from epididymal infection.

Clinical Findings

Tuberculosis of the genitourinary tract should be considered in the presence of any of the following situations:

(l) chronic cystitis that refuses to respond to adequate therapy, (2) the finding of sterile pyuria, (3) gross or microscopic hematuria, (4) a nontender, enlarged epididymis with a beaded or

thickened vas, (5) a chronic draining scrotal sinus, or (6) induration or nodulation of the prostate and thickening of one or both seminal vesicles (especially in a young man). A history of present or past tuberculosis elsewhere in the body should cause the physician to suspect tuberculosis in the genitourinary tract when signs or symptoms are present.

The diagnosis rests on the demonstration of tubercle bacilli in the urine by culture or positive polymerase chain reaction (PCR). The extent of the infection is determined by (1) the palpable findings in the epididymides, vasa deferentia, prostate, and seminal vesicles; (2) the renal and ureteral lesions as revealed by imaging; (3) involvement of the bladder as seen through the cystoscope; (4) the degree of renal damage as measured by loss of function; and (5) the presence of tubercle bacilli in one or both kidneys.

Treatment

Genitourinary tuberculosis is extrapulmonary tuberculosis. The primary treatment is medical therapy. Surgical excision of an infected organ, when indicated, is merely an adjunct to overall therapy.

Source:

1. Tanagho, McAninch - Smith's General Urology 18th edition

2. EAU Guidelines Urological Infections, 2016

3. ISKRA smjernice za liječenje urinarnih infekcija, 2014

Transplantation

The 50th anniversary of the first successful kidney transplant from a live donor to his identical twin was celebrated in 2004. During this interval, kidney transplantation has progressed from an experimental procedure to the preferred method of renal replacement therapy worldwide.

This is a result of continually improving outcomes producing a better quality of life, and a prolongation of survival compared to dialysis. At the end of 2005, in the United States, there were about 325,000 patients receiving renal replacement therapy, with an incidence rate of about 330 per million population.

Croatia, however, is one of the leading countries in solid organ transplantation in the world(!) and a respected member of the Eurotransplant organization. Eurotransplant is a non-profit international service organization that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs at the service of its member states.As mediator between donor and recipient, Eurotransplant plays a key role in the allocation and distribution of donor organs for transplantation. Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg and Slovenia are the eight countries cooperating within the Eurotransplant region. The deceased donor rate for kidneys in 2016 for Croatia was 27 per million population (pmp), and 43.7 pmp kidney transplants were performed in 2016, respectively.

Currently, 1- and 5-year kidney graft survival ranges between 89– 95% and 66–80%, depending on donor source. The major reasons leading to improved outcomes are more potent yet selective immunosuppression, better surgical techniques, more sensitive cross-matching, and better prophylaxis and treatment of morbid infections. There is also an emerging consensus

that preemptive transplantation, immediately prior to the need to dialysis, is advantageous in reducing much morbidity and even mortality.

SELECTION & PREPARATION OF RECIPIENTS

The most frequent diagnoses of renal failure leading to transplantation are diabetes 23% (the fastest growing); all types of glomerulo-nephritis/focal sclerosis 24%; hypertension-nephrosclerosis 16%; cystic kidney diseases 9%; interstitial/pyelonephritis 5%; urologic diseases 4%; and unknown causes 13%. Patients over age 65–70, the fastest growing recipient group, are commonly transplanted today as physiological age is considered more important than chronological age. Most patients with end-stage renal disease (ESRD) can be suitable transplant candidates with a few absolute contraindications. These include active infections or cancer, severe vasculopathy from atherosclerosis, and metabolic diseases likely to recur (oxalosis, cystinosis). However, all decisions must be individualized, and patients with a life expectancy of <3 years probably should be maintained on dialysis. Other factors such as psychosocial status, environment, and ability to follow a complex medical regimen are also important considerations. Prior to transplant, it is important to identify correctable conditions that may increase morbidity and diminish outcomes after the transplant.

A. GENITOURINARY TRACT EVALUATION

It is important that the native urinary tract will function properly after transplant, and an accurate *urologic* history is essential. Potential recipients without a history of urologic symptoms or prior interventions do not need an extensive evaluation. Upper tract ultrasound and urine cultures usually suffice; some recommend voided cytology and age-appropriate screening PSA in males. Patients with a history of urologic symptoms (especially hematuria, infections, stones, and incontinence), prior interventions, or a neurogenic bladder should have a full urologic evaluation including upper tract/pelvic imaging, a voiding cystogram, cystoscopy and retrograde studies, cytology, and, if indicated, a urodynamic study.

Upper Tract Abnormalities—Removal of the native kidneys, once advocated, is uncommon today and needed in 10% or fewer patients. Residual urine output and potassium excretion,

even if small, as well as production of erythropoietin and vitamin D3 via the retained kidneys are considered beneficial. Medical indications for nephrectomies are rare, and include heavy proteinuria (>10 g/day), intractable hypertension (4–5 drugs), and persistent hematuria. Kidneys with chronic hydronephrosis, high-grade reflux, stones, abscesses, filling defects, enhancing masses, complex or very large cysts, etc. that may lead to persistent infections or harbor potential cancers should be removed prior to transplant. In addition, very large polycystic kidneys may need removal for relief of symptoms or size considerations.

Lower Tract Abnormalities—It is important to remember that dialyzed patients often have a diminished urine volume, resulting in a small-capacity bladder with low compliance. Such bladders will resume normal function, even 25 years later, once urine volume is restored. However, small capacity bladders that are fibrotic and scarred from prior surgery, radiation, old TB, congenital anomalies (posterior urethral valves, meningomyelocele, etc.) will not recover. In these rare cases, often children, the preferred option is a bladder augmentation with bowel (ileum, stomach, colon, or dilated ureter) or a continent neo-bladder to produce a compliant reservoir with adequate volume. If the bladder is absent or destroyed, an ileal conduit can be created for transplantation. It is advisable that such major reconstructions be done and healed prior to transplantation.

B. INFECTION

Bacterial—Active infections are a contraindication to transplantation, which need to be appropriately treated and resolved. The urinary tract should be sterile for transplantation. Recurrent urinary tract infections require a full urologic evaluation including upper tract imaging, a voiding cystogram, cystoscopy, and retrograde studies. Recipients with a prior history of tuberculous disease or exposure should receive a year of isoniazid prophylaxis.

Viral—Herpes family DNA viruses such as cytomegalovirus (CMV), Epstein-Barr Virus (EBV), varicella zoster (VCZ), and herpes simplex (HSV) can be transmitted with the donor organ or reactivated from a latent state in the recipient. Therefore, recipients are usually given prophylaxis with a nucleoside inhibitor such as oral valganciclovir for 3 months, especially when they are seronegative and the donor is seropositive. Those patients with serologic evidence of prior hepatitis B or C exposure have diminished outcomes, especially if their liver

has evidence of cirrhosis. However, those recipients with inactive liver disease who have antibodies to either virus may receive organs from donors that are also positive for either hepatitis B core or hepatitis C antibody. Renal failure patients with active and untreated human immunodeficiency virus (HIV) should not be further immunosuppressed by transplant. However, those stable HIV-positive individuals treated with current antiretroviral drug therapy can do well for up to 5 years after kidney transplant.

C. MALIGNANT DISEASE

Active or recently recurrent malignant disease is an absolute contraindication to renal transplantation. The bulk of evidence suggests that immunosuppressive therapy facilitates the growth of residual cancers. The safe waiting period for transplantation after surgical removal of solid tumors varies and depends on the grade and stage of tumor on presentation and the associated risk of recurrence. The highest recurrence rates occurred with breast carcinomas (23%), symptomatic renal carcinomas (27%), sarcomas (29%), bladder carcinomas (29%), non melanoma skin cancers (53%), and multiple myeloma (67%).

Therefore, with some exceptions, a minimum waiting period of 2 years for cancers with a favorable prognosis is desirable. A waiting period of 5 years is desirable for lymphomas, most carcinomas of the breast, colon, or for large (>5 cm) symptomatic renal carcinomas. More recently it has been suggested that rather than using fixed waiting times, it is more logical to use cancer recurrence nomograms to establish risk. This has been well established for localized prostate cancer, where risk for recurrence can be compared to mortality risk on dialysis to establish an individualized assessment.

D. SYSTEMIC AND METABOLIC DISEASE

Patients with certain metabolic diseases affecting the kidney such as Fabry's disease, hemolytic uremic syndrome, vasculitis, systemic lupus erythematosus, amyloidosis, etc. as well as various forms of glomerulonephritis and focal sclerosis may experience recurrence, and patients should be counseled regarding this possibility. Those with severe metabolic stone disease that resulted in kidney loss will often experience recurrent stones and a poor outcome. A combined hepatic and kidney transplant is now commonly recommended for primary hyperoxaluria and less so for cystinosis .

E. CARDIOVASCULAR STATUS

Cardiovascular disease represents the leading cause of death after kidney transplantation and is ubiquitous among renal failure patients, especially diabetics and those over age 50. Potential recipients should be thoroughly screened, and have symptomatic lesions corrected prior to transplant since those with ESRD are at high risk for ischemic events. Since many dialysis patients are sedentary, already have abnormal EKG patterns, and diabetics may not experience angina with exertion, provocative stress tests are necessary. However, subjects should reach their target heart rate for these tests to have an accurate predictive value. If any uncertainty exists, the gold standard remains coronary angiography. Patients with a history of strokes or transient ischemic attacks should be screened with a carotid ultrasound and receive neurology clearance. Those with adult polycystic kidney disease need a brain MR angiogram to screen for aneurysms. Peripheral vascular disease is common in renal failure, especially diabetics, and ultrasound screening can be helpful. A pelvic CT scan without contrast can be helpful to determine the degree of calcification of the pelvic vessels and aid in kidney placement. Active claudication, femoral bruits, or diminished pulses demands a complete vascular surgical assessment.

F. GASTROINTESTINAL DISEASE

Patients with ESRD often have a history of gastrointestinal (GI) problems such as peptic ulcer disease, gastroesophageal reflux, cholecystitis, pancreatitis, inflammatory bowel disease, diverticulosis, chronic diarrhea or constipation, or hemorrhoids. If present, these should be evaluated and resolved prior to transplant. Upper or lower GI endoscopy and/or contrast imaging of the bowel may be required.

Obesity—In North America obesity is affecting a greater number of patients with renal failure each year. Numerous reports have identified obesity (BMI >30 kg/m2) and morbid obesity (BMI >35 kg/m2) as an independent risk factor for increased cardiovascular mortality, decreased graft survival, delayed graft function (DGF), wound complications, posttransplant diabetes, proteinuria, and prolonged hospitalization. Weight reduction to under the morbidly obese range is desirable, and may require bariatric surgery in extreme circumstances.

Smoking—Tobacco smoking is particularly deleterious for transplant recipients, and patients need to stop prior to transplantation. Smoking both accelerates the progression of atherosclerotic cardiovascular disease and is nephrotoxic to the kidney resulting in proteinuria.

I. TRANSPLANT ALLOGRAFT NEPHRECTOMY

After a failed transplant, immunosuppression is weaned off and the patient returns to dialysis. If graft loss occurs after a year it is usually not necessary to remove the failed graft, as a new kidney can be placed on the contralateral side. In a few cases, when graft failure is early or is due resistant rejection, the kidney tissue may undergo necrosis and the graft needs to be removed. Indications for allograft nephrectomy include fevers, graft tenderness, gross hematuria, malaise, infection, and uncontrolled hypertension. The subcapsular allograft nephrectomy is the safest approach to prevent iliac vessel injury.

SELECTION OF DONORS

Living Donors

A. DIRECTED LIVING KIDNEY DONORS

Living kidney donation provides a better patient and allograft survival when compared with deceased-donor transplantation, especially when the live donor tranplant is performed before the onset of dialysis. In the United States, the annual number of live kidney donors has surpassed the number of deceased donors since 2001, although the absolute number of transplants from deceased donors still outnumbers those from living donors (LDs). Based on tissue typing disparities (HLA mismatches), an immunologic hierarchy can be established for the best “match”. The advantages for identical twins and HLA identical siblings are quite significant; while all other live donor combinations are similar and provide significant advantages to the deceased donor.

B. NONDIRECTED LIVING KIDNEY DONORS

The extreme shortage of kidneys to meet the demand of waiting recipients coupled with the success of LURD kidney transplantation has opened up creative ways to expand the pool of

live donors. In particular, there are individuals who wish to be anonymous donors, ie, "nondirected or altruistic donor." However, in the United States, living-donor exchanges must adhere to Section 301 of the National Organ Trans- plant Act of 1984 (NOTA), which states, "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation." Valuable consideration according to this act has traditionally been considered to be monetary transfer or a transfer of valuable property between the donor and the recipient. The donation of an organ is properly considered to be a legal gift. With these constraints any person who is competent, willing to donate, free of coercion, and found to be medically and psychosocially suitable may be a live kidney donor. Three protocols of nondirected living donation have been developed to accommodate such donors: (1) a live- donor paired exchange, (2) a live-donor/deceased-donor exchange, and (3) altruistic donation.

C. LIVING DONOR SAFETY

From its inception, the removal of a kidney from a healthy individual to benefit another has been problematic. The practice is based upon the belief that the removal of one kidney does not diminish survival or significantly harm long-term kidney function. This notion derives from follow-up of patients up to 45 years after nephrectomy for trauma, and after kidney donation. Unilateral nephrectomy caused an average decrease of 17 mL/min in the GFR that tended to improve with each 10 years of follow-up (average increase 1.4 mL/min/decade). A small, progressive increase in proteinuria was also noted (average 76 mg/decade) but was negligible after nephrectomy for trauma or kidney donation, and nephrectomy did not affect the prevalence of hypertension. Thus, the published evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy. The rate of ESRD in kidney donors was calculated to be 0.04%, comparable to the rate of ESRD in the general US population (0.03%).

Deceased Donors

A diagnosis of brain death is required in a comatose subject who may potentially be a deceased organ donor. Most organ donors have severe brain injury and present to the hospital with a low

Glasgow Coma Scale score. Most deceased organ donors are brain dead. Proper diagnosis of brain death is essential to the organ donation process and to maintaining public trust and acceptance of organ donation from brain-dead organ donors. Among the lay public, there is often a troubling confusion between the diagnosis of brain death and that of a persistent vegetative state. The criteria for diagnosis and declaration of brain death are well described and require irrefutable documentation. They include a known cause of brain injury, irreversibility, and absence of cerebral and brainstem function, including apnea. The diagnosis of brain death should be made by a physician who is independent of the transplantation team and thus free of conflict of interest. Ancillary testing is not mandated but may include electroencephalography, conventional angiography, radionuclide angiography, magnetic resonance angiography, computed tomographic angiography, transcranial Doppler, and somatosensory evoked potentials. Indications for pursuit of ancillary testing include toxic drug levels, inconclusive apnea testing, normal neuroimaging, inability to complete a clinical examination, and chronic CO_2 retention. The potential donor must be evaluated for any transmissible pathological condition and the quality of any organ(s) being considered for transplantation.

The imbalance between the supply of brain-dead deceased donors and the growing demand for kidneys has created many innovative uses of organs that were excluded in the past. These generally include kidneys from donors over the age of 60, the presence of systemic disease such as atherosclerosis, hypertension or early diabetes, donors with cardiac arrest or significant hypotension, and some with prior exposure to virus and/or infections that have resolved. While kidneys that are severely traumatized or come from donors with active cancer, sepsis, or HIV-AIDs, are excluded, a number of donor organs with extended criteria that convey about a 10% worse overall graft survival have been incorporated into the donor pool.

EXTRACORPOREAL RENAL PRESERVATION

1. Simple hypothermic storage and flush solutions — Once removed, kidneys are flushed and stored in a hyperosmolar, hyperkalemic, and hyponatremic solution at (4–10° C) to minimize ischemic injury (cellular swelling). This is usually sufficient for up to 24 hours of

preservation although longer cold ischemic times (up to 40 hours) have been reported, but result in higher rates of delayed graft function (DGF). A commercial storage solution from the University of Wisconsin is frequently used, which contains inert substrates like lactobionate, raffinose, hydroxyethylstarch, and adenosine as an energy substrate. Recently, a less viscous alternative Histidine-Tryptophan-Ketoglutarate (HTK) solution has been shown to yield similar results with cold ischemia times <and> 24hours.

2. Pulsatile perfusion — Hypothermic pulsatile perfusion is an alternative method of preservation, which takes advantage of a continuous pulsatile flow through the graft. Some feel such hydrodistention is therapeutic in dilating the ischemic renal microcirculation, and permits the delivery of vasodilator drugs (ie, verapamil, beta-blockers). It also permits measurement of flow, pulse pressure, and resistance through the graft, which is an accurate method to determine viability of the kidney. Pulsatile perfusion is more costly and requires investment in a preservation unit and a technologist, but has been gaining popularity due to the increasing number of expanded criteria donors that are considered for transplant.

THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

Tissue Typing

The MHC describes a region of genes located on chromosome 6 in man which encode proteins that are responsible for the rejection of tissue between different species or members of the same species. The cell surface MHC markers are called human leukocyte antigens, because they were first identified on white blood cells. There are two major types of HLA antigens termed class I and class II. Virtually all nucleated cells express HLA class I antigens, while class II antigens are primarily found on B cells, monocytes, macrophages, and antigen-presenting cells. Each individual inherits two serologically defined class I (called A and B) and one class II (called Dr) antigen from each parent; so six HLA antigens constitute an individual's tissue type. One set of HLA A, B, and Dr antigens inherited from a parent is called a haplotype, so that HLA-identical siblings have inherited both haplotypes. The HLA molecules are polymorphic (over 150 defined), so it is very unusual if two unrelated individuals have the same tissue type of six HLA antigens. HLA antigens not shared between two individuals will

generate an immune response. Therefore, the term HLA matching describes the number of shared antigens. One can generate a hierarchical rating of genetic HLA similarities, which roughly correlate to the risk for rejection and eventual kidney transplant outcomes ranging from identical twins to DD. In clinical practice, the impact of HLA on graft survival is small the first years, but plays an important role after 5–10 years. No doubt other factors affect survival; especially donor organ quality (age, function, size, etc.) as well as recipient age and comorbidities. In addition, HLA antigen matches also play a role in the algorithm for distribution of deceased donor kidneys with more points assigned for better matches.

Cross-matching

Preformed circulating anti-HLA antibodies against the specific phenotype of the donor will lead to acute (if not hyperacute) rejection. Such antibodies (usually IgG) are detected by cross-matching the sera of the recipient with lymphocytes of the donor and adding complement. Such complement-dependent cytotoxicity (CDC) will kill the donor cells and is indicative of deleterious clinical outcome. A similar yet more sensitive test has been developed using flow cytometry to identify the presence of anti-HLA antibodies bound to the surface of donor lymphocytes. A cross-match against both donor T and B lymphocytes is performed within 24 hours of surgery, and transplants are not done if these antibodies are present. In addition, the ABO system will trigger CDC against the mismatched blood group antigens (glycoproteins) present on many tissues. Therefore, transplants are usually done only between ABO-compatible individuals.

Serum Screening

At monthly intervals waiting patients have their serum screened for the presence of anti-HLA antibodies against a panel of HLA phenotypes (lymphocytes) that represent the general population. The result is reported as a percent of the total referred to as percent reactive antibody (PRA). Those with high titers (>50%) of anti-HLA antibody against the broad population are said to be sensitized and will find it very hard to find a cross-match-negative donor. Sensitized patients waiting for an organ depend on better HLA matches to find a cross-match-negative

donor. Sensitization to HLA can occur from prior blood transfusions, viral infections, pregnancy, or previous transplants.

Posttransplant Antibodies

The development of de novo donor-specific or non-donor-specific anti-HLA antibodies after the transplant has a deleterious effect on outcomes. Both a greater frequency of acute and chronic rejection as well as lower graft survival have been reported among those patient with these antibodies detected by flow cytometry. The presence of these antibodies may identify those recipients that need more rather than less immunosuppression.

LIVING DONORS

1. *Evaluation*

All donors should be evaluated both medically and surgically to ensure donor safety. First a thorough history and physical exam is needed to rule out hypertension, diabetes, obesity, infections, cancers, and specific renal/urologic disorders. Then laboratory testing of blood and urine, chest X-ray, electrocardiogram, and appropriate cardiac stress testing is done. Different methods to measure GFR and urine protein excretion are incorporated. Finally, radiographic assessment of the kidneys and vessels is ordered, which is usually accomplished by a CT angiogram. A catheter angiogram is reserved for complex anatomy. The donor is always left with the better kidney. If the two kidneys are equal, the left is preferred for transplant due to its longer and often thicker renal vein. However, in cases when one kidney has multiple renal arteries, the kidney with the single artery is selected. In younger fertile female donors, concern about physiologic hydronephrosis of the right kidney is taken into consideration.

2. *Surgical technique*

Today, the most commonly used approach is intraperitoneal laparoscopic donor nephrectomy, primarily due to patient choice. This technique has all but supplanted open donor nephrectomy via an extraperitoneal flank incision due to reports of reduced pain and shorter recovery time. An alternative is the hand-assisted laparoscopic approach, where the extraction incision is used during the dissection. When multiple renal arteries are encountered, they should be conjoined ex vivo while the kidney is on ice, in order to minimize the number of anastomoses in the recipient and reduce ischemia times. Smaller upper pole arteries (<2mm) often can be sacrificed, while lower pole vessels should be retained because of a risk to the ureteral blood supply.

DECEASED DONORS

Today, most donors are multiple-organ donors, and they require removal of the liver, heart and lungs, and pancreas, in addition to the kidneys. The retrieval needs to be coordinated and is often performed by several teams representing each organ for transplant. Usually the thoracic organs are removed first while the abdominal organs are cooled and perfused with UW or HTK perfusion solution. The kidneys are removed en-bloc with the aorta and vena cava and a large amount of retroperitoneal tissue. They are separated on the back bench by dividing the great vessels with the renal vessels attached.

STANDARD RENAL TRANSPLANT SURGERY

There are several different methods for surgical revascularization of the kidney. While either iliac fossa is acceptable for the transplant, the right side is often preferred due to the longer and more horizontal segments of external iliac artery and vein compared to the left side. A lower quadrant curvilinear (Gibson) incision is made, and the iliac vessels are exposed through a retroperitoneal approach. The renal-to-iliac-vein anastomosis is usually performed first, in an end-to-side fashion with 5-0 nonabsorbable monofilament suture. The renal artery can be anastomosed end-to-end to the internal iliac using 6-0 nonabsorbable monofilament suture. However, in older recipients and diabetics this vessel often has significant arterial plaque causing poor runoff. In addition, concern about compromising arterial flow to the penis via the pudendal artery with subsequent erectile dysfunction limits this approach in older males. Because of these factors, an end-to-side anastomosis of the renal artery to the external iliac artery is more frequently done with 6-0 nonabsorbable monofilament suture. An extravesical ureteroneocystostomy is the preferred method to reimplant the ureter. When healthy-appearing ureter is short or the bladder is defunctionalized and small, a native to transplant uretero-ureterostomy can be done. An internal double J ureteral stent is always placed; and a closed suction drain is left in the deep pelvis.

IMAGING OF THE TRANSPLANT KIDNEY

Immediately after the transplant, it is advisable to obtain a baseline duplex Doppler ultrasound to confirm patency of the renal vessels, blood flow to the parenchyma, and to identify large fluid collections, hematomas, or hydronephrosis. This is especially important when the graft is oliguric. Similar information can be obtained using an isotopic (mercaptoacetyltriglycerine, 99mTc-MAG-3) renal scan. Kidneys with DGF demonstrate atypical pattern of isotopic uptake with little clearance or excretion. If fluid collections or intraperitoneal problems are suspected, finer definition can be obtained with a CAT scan. The use of 3-DCAT scans or MR angiography can delineate actual vascular lesions (stenoses, aneurysms, a-v fistula). Catheter angiography is reserved for interventions that require access to the renal vessels such as

angioplasty. Imaging with IV-iodinated contrast should be limited when the creatinine is elevated, but cystograms and antegrade nephrostograms can be helpful to identify urinary fistulas or obstructions.

IMMEDIATE POSTTRANSPLANT CARE

A. HEMODYNAMIC MANAGEMENT

Initial postsurgical care the first hours and days focuses on the urine output and eventual recovery of GFR. It is important to avoid hypotension, dehydration, or use of alpha-adrenergic drugs, which will exacerbate surgical and preservation injury. It is helpful to monitor central venous pressures to maintain adequate preload (10–15 cm water). Urine outputs >1cc/kg/hr are desirable, and hourly IV replacementat cc/cc of urine is usually sufficient. Some live donor kidneys may generate outputs up to a liter per hour, which will drop the blood pressure and should be managed with only 1/2–2/3 volume replaced. Alternatively, fluid overload and pulmonary edema may cause renal hypoperfusion and should be avoided. Treatment with fluid restriction, diuretics, and even dialysis may be needed. Even when hemodynamically stable, many DD recipients (and a few LD recipients) will experience delayed recovery of graft function, which is a consequence of extended cold preservation times, warm ischemia in the donor, or prolonged anastomosis time in the recipient.

B. DELAYED RECOVERY OF GRAFT FUNCTION

DGF is more formally defined as the need for dialysis the first week after transplant and occurs in about a third of DD recipients. Patients with DGF may produce liters of urine a day (non-oliguric DGF), but have a rising creatinine level and need dialysis. Others produce under 300cc a day of urine and are described as oliguric, which is usually an indication of a more prolonged recovery time. These clinical events are associated with specific histological findings referred to as acute tubular necrosis (ATN), the hallmark of which is tubular epithe- lial swelling, necrosis, and regeneration with mitotic figures. If kidneys are in oliguric DGF for over a week and imaging studies demonstrate good blood flow, a biopsy should be done to rule out rejection and confirm ATN. Transplant DGF resolves in most cases, but may take up to several weeks;

while about 1–2% of grafts never function (primary nonfunction). DGF does have a negative impact on both short- and long-term graft survival compared to kidneys that function immediately. During DGF it is helpful to delay the introduction of calcineurin inhibitor (CNI) drugs for 7–10 days until some recovery of function is evident. This usually requires the use of an induction antibody as an umbrella of protection until the graft heals.

C. SUDDEN DROP IN URINE OUTPUT

During the first few days, a sudden loss of urine output after an initial diuresis demands prompt attention to ensure patency of the Foley catheter, and if easily obtainable, a repeat ultrasound to confirm vascular flow and exclude hydronephrosis. If there is any question of abnormal blood flow or a delay in obtaining an imaging study, the kidney should be promptly reexplored since vascular compromise of a few hours will result in allograft necrosis. Loss of urine output from the bladder catheter with increased drain output may suggest a urine fistula. The drainage fluid can be sent for creatinine, and if 5–10 times the serum level suggests urine. If the above problems are excluded with imaging studies, renal biopsy is needed to rule out acute rejection or thrombotic microangiopathy, and to ensure graft viability.

TRANSPLANT REJECTION

The disparate HLA phenotypes on donor tissue trigger an immune response that leads to renal dysfunction and histological changes in the transplanted kidney called rejection. These responses are both humoral and cellular, and depend upon the presentation of processed donor HLA antigens via either donor (direct) or host (indirect) antigen-presenting cells to the recipient’s immunocompetent T cells. The clinical signs and symptoms of acute renal allograft rejection include fever, chills, lethargy, hypertension, pain and swelling of the graft, diminished urine output, edema, an elevated serum creatinine and BUN, and proteinuria. Immunosuppression is designed to prevent these events. Rejection can also be divided in three distinct clinical entities based on the timing and mechanism responsible for triggering these events.

Hyperacute rejection

occurs immediately after revascularization of a kidney when preformed cytotoxic anti-HLA antibody is present. It will lead to graft thrombosis, and the kidney must be removed. While there is no treatment, it can be prevented almost completely by using the sensitive cross-matching techniques available today.

Acute rejection

episodes can occur at anytime after the transplant, but most occur in the first 3 months. Such episodes can be mild or severe and cause the symptoms previously described to a variable degree. With the currently available immunosuppression about 20% or less of transplant recipients experience acute rejection and most episodes are reversible with treatment. Less than 5% of recipients lose their graft due to unresponsive acute rejection. These episodes are predominantly cellular and cause graft infiltration of cytotoxic cells, but humoral mechanisms contribute to the process.

Chronic rejection

defines a process of gradual, progressive, decline in renal function over time. It is associated with hypertension and proteinuria, and is accompanied by histological features of tubular atrophy, interstitial fibrosis, and an occlusive arteriolopathy. It can be detected as early as 6 months after transplant, and is thought to have a strong humoral response against the graft. Some, but not all recipients have had prior acute rejections or have donor-specific antibody detected. There is a role for alloimmunity (antigen dependent factors), since it does not occur in identical twins, is rare in HLA-identical sibling transplants, and is most common among DD recipients. However, many of these histologic changes are found with older donor age, ischemic injury, viral infections, and other systemic comorbidities, referred to as antigen-independent factors. Therefore the process remains less well characterized, is no doubt multifactorial, and is often given the name chronic allograft nephropathy (CAN). Treatment is often not effective, and consists of tight control of blood pressure, the use of ACE/ARB drugs for proteinuria, and sparing or elimination of CNI drugs.

The goal in transplantation is to develop methods that permit a recipient to keep a transplanted organ in a state of "tolerance" or donor-specific unresponsiveness. Until that day arrives, clinical practice is dependent on our ability to interrupt the host immune response using agents that are not precise. It is a constant struggle to deliver enough immunosuppression to prevent rejection, but not too much to render the patient susceptible to infections and cancers. In addition, immunosuppressive drugs have unique mechanisms of action and their own specific toxicities. Immunosuppressive agents can be used in one of three ways: (1) high dose or induction therapy to prevent a primary immune response immediately after transplantation, (2) low dose or maintenance therapy initiated once the graft function has stabilized, or (3) additional high dose therapy to treat acute rejection.

CHEMICAL IMMUNOSUPPRESSION

Corticosteroids

Since the initial observations more than 40 years ago that corticosteroids could prevent and treat renal allograft rejection, they have become the cornerstone of immunosuppressive therapy. Corticosteroids have numerous effects on the immune system that include sequestration of lymphocytes in lymph nodes and the bone marrow resulting in lymphopenia. Glucocorticoids become bound to intercellular receptors, and conformational changes in the steroid-receptor complex that interferes with cytokine production. Their primary immunosuppressive effect is inhibition of monocyte production and release of interleukin (IL-1), with subsequent inhibition of T cell IL-2 and interferon-gamma; thus interfering with lymphocyte activation and production of effector cells. However, systemic toxicities of steroids are myriad; including cushingoid features, hypertension, hyperlipidemia, hyperglycemia, weight gain, osteoporosis, poor wound healing, growth retardation, psychiatric disturbances, etc. and have resulted in intense efforts to reduce steroid dosage. Alternate-day steroid dosing appears beneficial for growth in children, but complete steroid withdrawal or avoidance has become more appealing. The benefits include lower blood pressure, improved lipid profiles, and diminished physical side effects attributed to steroids. There have been several reviews of

trials attempting to withdraw steroids form stable transplant patients. Early graft stability is often followed by acute rejection requiring the reintroduction of steroids. If attempted, withdrawal should be entertained in well-matched recipients, 1 year or more after transplant, with no prior episodes of rejection.

Antiproliferative drugs

Azathioprine — Introduced first in the 1960s, 6- mercaptopurine and its imidazole derivative azathioprine represent antimetabolites that blocks purine biosynthesis and cell division. The developers of azathioprine, Gertrude Elion and George Hitchings, received the 1988 Nobel Prize. Azathioprine is most effective if given immediately after antigen presentation to prevent rejection and is ineffective in treating established rejection. Adverse effects of azathioprine include bone marrow suppression (primarily leukopenia), alopecia, hepatoxicity, and increased risk of infection and neoplasia. When compared directly with another antiproliferative agent, mycophenolate mofetil (MMF), azathioprine is not as potent in rejection prophylaxis. Therefore, its use has been diminishing rapidly over the past few years, but serves as a secondary agent replacing MMF for intractable toxicity.

Mycophenolate mofetil — MMF is a morpholinoethyl ester of the fungal antibiotic mycophenolic acid, which is a noncompetitive inhibitor of the enzyme inosine monophosphate dehydrogenase. MMF inhibits purine biosynthesis preventing the proliferation of activated T and B cells, thereby blocking both cellular and humoral immune responses. It is thought to be more specific for those lymphocytes that rely primarily on de novo purine synthetic pathways, and has replaced azathioprine as an antimetabolite. MMF is usually well tolerated at dosages up to 2 g (divided dosing), with GI disorders (nausea, vomiting, cramps, and diarrhea) and bone marrow suppression (leukopenia, anemia) being its major toxicities. Recently therapeutic drug monitoring of blood levels have been reported to address interpatient variability, efficacy, and some reduction in GI toxicity.

Antilymphocytic drugs

Calcineurin inhibitor drugs

Cyclosporine, a lipophilic small molecule, has been the cornerstone of transplant immunosuppression since the early 1980s and is the prototype CNI drug. It binds to a specific intracellular immunophilin (cyclophilin) causing conformational changes and subsequent engaging of the enzyme calcineurin phosphatase; thereby preventing the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation. The adverse effects of cyclosporine, which are related to the concentration of the drug, include nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and the hemolytic uremic syndrome. CNI drugs are metabolized by the hepatic cytochrome P-450 (3A4) system, and other drugs that inhibit or stimulate this enzyme system (ie, diltiazem and ketoconazole, orphenytoin and isoniazid) can significantly affect blood levels, thus favoring therapeutic drug monitoring. Recent developments include monitoring of the peak cyclosporine levels 2 hours after administration to better reflect exposure to the drug. A microemulsion that exhibits more reproducible absorption and metabolism has replaced the initial oral formulation.

Tacrolimus is another CNI drug that engages a different immunophilin, FK-binding protein 12 (FKBP-12), to create a complex that inhibits calcineurin with greater molar potency than does cyclosporine. Some centers report better rejection prophylaxis with tacrolimus, but recent analyses suggests that with the current dosing strategies the efficacy of cyclosporine and tacrolimus are similar. Tacrolimus can also result in nephrotoxicity and the hemolytic uremic syndrome. It is more likely to induce new onset diabetes after transplant and neurological irritability (seizures, tremors). Compared to cyclosporine it seems less likely to cause hyperlipidemia, hypertension, and cosmetic problems. The use of tacrolimus has increased steadily and is now the dominant CNI, but many transplantation programs selectively use both agents, depending on individual patient risks. Hypertension, hyperlipidemia, and cosmetic changes argue for tacrolimus, whereas a high risk of diabetes (eg, older age or obesity), seizure risk argues for cyclosporine. However, the most distressing feature of continuous CNI use is acute and chronic nephrotoxicity. Acute CNI nephrotoxicity is mediated by pronounced vascular and to a lesser degree tubular alterations, manifested by oligo-anuria and azotemia, with associated hyperkalemia, hyperuricemia, hypertension, hypomagnesia, and renal tubular

acidosis. A dose-dependent reduction in renal blood flow and glomerular filtration is well documented. Chronic CNI nephrotoxicity is more insidious, associated with progressive deterioration of graft histology (scarring) in over 50% by 5 years and virtually all treated patients by 10 years. Dosage reduction will often mitigate against some these effects, and numerous regimens have been tested to try to minimize or eliminate CNI drugs; although it must be done carefully to avoid increased risk of rejection. Calcium channel blockers are often used to ameliorate CNI nephrotoxicity due to their ability to reduce the dosage requirements, treat the associated hypertension, and reverse the calcium-dependent afferent arteriolar vasoconstriction.

Target-of-rapamycin inhibitors

Sirolimus and everolimus form a class of immunosuppressive agents that have similar molecular structure to the CNIs, and bind to the same immunophilin protein (FKBP-12) as tacrolimus. However, their mode of action appears to be distinct, as the sirolimus complex does not inhibit calcineurin. Instead, the sirolimus-FKBP complex appears to engage a distinct p70 kinase called mTOR (molecular target of rapamycin). The inhibition of mTOR blocks IL-2 signal transduction pathways that prevent cell-cycleprogression from G to S phase inactivated Tcells. The principal non immune toxic effects of sirolimus and everolimus include hyper lipidemia, marrow suppression, and impaired wound healing and lymphoceles. Other reported side effects include delayed recovery from ATN, reduced testosterone concentrations, aggravation of proteinuria, mouth ulcers, and pneumonitis. However, sirolimus and everolimus may reduce CMV disease. Sirolimus and everolimus were developed for use with cyclosporine, but the combination increased nephrotoxicity, the hemolytic–uremic syndrome, and hypertension. Sirolimus has been combined with tacrolimus, but this combination also produced renal dysfunction and hyperten- sion; which indicates that sirolimus potentiates CNI nephrotoxicity. TOR inhibitors may have antineoplastic and arterial-protective effects.

ANTILYMPHOCYTE ANTIBODIES

1. Polyclonal antibodies

Polyclonal antibodies are produced by injecting (immunizing) animals such as horses, goats, sheep, or rabbits with cells from human lymphoid tissue. Immune sera from several animals are pooled and the gamma globulin fractions extracted and purified. A rabbit-derived antithymocyte antibody (Thymoglobulin, Genzyme) is the most frequently used preparation. Once injected, the antibodies bind to lymphocytes resulting in a rapid lymphopenia or depletion due to complement-mediated cell lysis; as well as masking of surface antigens or induction of suppressor populations that block cell function. Polyclonal antibodies have been used primarily in cadaveric renal transplantation, initially as induction therapy, and to treat vascular or antibody-mediated rejection. Because of their strong immunosuppressive effects, polyclonal antibodies are limited to short courses of 3–10 days, but their depletion may last 6–12 months. Adverse effects include fever, chills, and arthralgias related to the injection of foreign proteins and the release of cytokines. These effects can be minimized by pretreatment with corticosteroids and antihistamines. More serious adverse effects include increased susceptibility to infections (especially viral), and neoplasia.

2. Monoclonal antibodies that deplete lymphocytes

The introduction of murine hybridoma technology opened the door to the development of highly specific antibodies directed against functional cell surface targets. These antibodies, like polyclonal antibodies, exert their effects through a variety of immune mechanisms. In addition to complement-mediated lysis, blockade and inactivation of cell surface molecules, and opsonization with phagocytosis, these antibodies can induce cytotoxicity and modulation of cell surface molecules on target tissues.

Muromonab-CD3 — Muromonab-CD3, a mouse monoclonal antibody against CD3, was the first commercially available monoclonal antibody used in transplantation for induction and to treat rejection. Muromonab-CD3 binds to the T-cell-receptor-associated CD3 complex, which first triggers a massive cytokine-release syndrome before both depleting and functionally modulating T cells. Humans can make neutralizing (human antimouse) antibodies against muromonab-CD3 that terminate its effect and limit its reuse. Adverse effects from a typical 5-

mg dose include a first-dose response that simulates a severe flu-like syndrome, consisting of fever, chills, nausea, vomiting, diarrhea, myalgias, headache, and in severe cases, aseptic meningitis and pulmonary edema. These effects can be minimized (but not eliminated) by pretreatment with corticosteroids and antihistamines. Prolonged courses of muromonab-CD3 increase the risk of posttransplantation lymphoproliferative disease (PTLD). The use of muromonab-CD3 has declined due to the introduction of humanized and/or chimeric antibodies that are better tolerated.

Rituximab—Rituximab is a chimeric anti-CD20 monoclonal antibody that eliminates most B cells, and was initially approved for treating refractory non-Hodgkin's B-cell lymphomas. Interestingly it was introduced in transplantation to treat a similar tumor, PTLD. Rituximab is currently being evaluated to treat donor-specific alloanti- body responses such as antibody-mediated rejection or in transplanting sensitized recipients. It is used in combina- tion with maintenance immune suppressive drugs, plasma- pheresis, and intravenous immuneglobulin. While plasma cells are usually CD20-negative, some precursors are CD20-positive and their elimination may reduce some antibody responses. Such therapy may provide the first of future tools to control humoral rejection.

3. Monoclonal antibodies that are nondepleting

Daclizumab and basiliximab — Another selective site for monoclonal antibody targeting of the immune response is the IL-2receptor (CD25), present on the surface of activated T cells and responsible for further signal transduction and T-cell proliferation. Both a chimeric (basiliximab) and a humanized (daclizumab) anti-CD25 have been genetically engineered to produce a hybrid IgG that retains the specific anti-CD25 binding characteristics with a less xenogenic (murine) backbone. These agents cause minimal cytokine release upon first exposure, and exhibit a prolonged elimination half-life resulting in weeks to months of CD25 suppression. Because expression of CD25 (interleukin-2 receptor *a* chain) requires T-cell activation, anti-CD25 antibody causes little depletion of T cells. Anti-CD25 antibodies are useful as safe induction agents in low- to moderate-risk recipients, but have little effect in treating an established rejection episode. Their use appear to offer a favorable risk-benefit compared to depleting agents, providing for improved graft survival with a lower risk of posttransplant cancers.

Belatacept — Basic immunology generated the concept that blocking costimulation (signal2) could prevent the activation of antigen-primed T cells, thus providing a new avenue for control of allograft rejection. A first generation of monoclonal antibodies designed to block costimulation proved the concept in animals, but lacked sufficient efficacy in initial clinical trials. Belatacept is a second-generation cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) immunoglobulin, engineered as a fusion protein combining CTLA-4 with the Fc portion of an IgG molecule. This biological agent engages CD80 and CD86 on the surface of antigen presenting cells, thereby blocking costimulation through T cell CD28. The one-year results of a phase2 trial in renal transplant recipients given MMF, steroids, and anti- CD25 antibody demonstrated that belatacept was as effective as cyclosporine in preventing acute rejection. If proven durable the use of a nondepleting bio- logical agent tocontrol rejection is a novel form of therapy that may be desirable for many patients. Belatacept is given at intervals of 2–4 weeks as an intravenous preparation, which may be limiting. A subcutaneous preparation of belatacept is under development.

TREATMENT OF REJECTION

Acute rejection leads to graft injury and eventual CAN if untreated. Therefore, it requires prompt and accurate diagnosis, which is best provided from a percutaneous transplant renal biopsy often done under ultrasound guidance. One of the remarkable achievements of the last 10 years has been the universal acceptance of the Banff Schema to diagnose and characterize renal allograft rejection. The scoring system is semiquantitative, based on light microscopy, and describes features for acute rejection and chronic/sclerosing nephropathy as well as features attributed to both cellular and antibody-mediated mechanisms. For patients with Banff I or II acute rejections, high-dose IV steroid pulses of 5–7 mg/kg/day for 3 days will reverse about 85%. Some clinicians also prefer to add a 10– 14 day recycle of oral prednisone at 2 mg/kg tapered to baseline. If rejections are unresponsive to steroids or histology confirms a component of Banff II or III vascular changes, a depleting antibody such as thymoglobulin is given at 7–8mg/kg over a week. If repeat flow cross-matching identifies a new donor-specific antibody, more extensive

treatments such as plasmapheresis, blocking IV immune globulin (2g/kg), or even anti-CD20 monoclonal antibody (Rituximab) can be used. It is not generally prudent to treat more than 2–3 acute rejections in anyone recipient.

RESULTS OF KIDNEY TRANSPLANTATION

There have been dramatic improvements in short-term kidney transplant outcomes since the inception of clinical practice 4 decades ago. For recipients of LD kidneys 1-year patient and graft survival has increased to about 97.6% and 95.1%; and for DD recipients 94.5% and 89%. The major reasons for this improvement are a reduction of acute rejection episodes (better immuno-suppression and cross-matching techniques) with fewer complications from its treatment; and better prophylaxis and treatment of the common posttransplant infections. However, long-term graft loss beyond 5–10 years has not changed much, with stagnant survival half-lives of 7–8 years for DD and 10–11 years for LD kidneys. A multifaceted process of graft scarring resulting in decline of function termed chronic allograft nephropathy (CAN) developes over time, which is the major reason for late graft loss. The etiologies of CAN include processes that are immune related as well as those associated with nonspecific renal injury. The second leading cause of late graft loss is death with a functioning graft, primarily due to the consequences of atherosclerotic cardiovascular disease; less so infections and cancers. Some risk factors for CAN and cardiovascular disease overlap (hypertension, hyperlipidemia, smoking, diabetes, etc). Graft loss secondary to patient noncompliance with medications has been estimated at 5–10%.

Complications of Kidney Transplantation

A. SURGICAL

The majority of significant surgical problems posttransplant are either vascular or urologic. They include renal artery thrombosis, disruption, stenosis, or mycotic aneurysm; renal vein thrombosis or disruption; urinary fistula or ureteral stenosis; lymphocele or hematoma; scrotal hydrocele or abscess; wound abscess, dehiscence, or hernia. Prevention is the best way to avoid these problems using meticulous surgical and antiseptic techniques, including the routine use of preoperative broad-spectrum antibiotics.

1. Vascular problems — In the early posttransplant period, vascular problems may prevent a new kidney from ever functioning, and questions raised from imaging studies often require surgical re exploration. Anastomotic bleeding requires immediate repair; twisting or compression of the vessels may require reanastomosis, while complete thrombosis necessitates nephrectomy. Early large hematomas should be surgically drained and hemostasis obtained. Significant transplant renal artery stenosis can occur from poor surgical technique, damage of the vessel intima at procurement, atherosclerosis or fibrous disease, or immune injury, but is fairly uncommon (1–5% of transplants). Poorly controlled hypertension, renal dysfunction (especially after ACE inhibitors or beta-blockers), or a new pelvic bruit are clinical clues. Percutaneous transluminal angioplasty is the treatment of choice and restores kidney perfusion in 60–90% of cases. The risk of restenosis can be minimized with an internal stent. Pseudoaneurysms of the renal or iliac artery and a-v fistula after biopsy are often amenable to embolization or endovascular stenting. Large >5 cm or mycotic aneurysms, inability to dilate a vascular stenosis, or unusual lesions may require open operative repair to prevent rupture.

2. Urologic problems — Urologic complications are reported in 2–10% of kidney transplants, and usually do not result in graft loss if promptly treated. It is advisable to leave a Foley catheter for 10–14 days for thin-walled, poorly vascularized, or small defunctionalized bladders. Ureteral fistulas and stenoses are usually a consequence of ischemia to the distal ureter from surgical dissection, overzealous electrocautery, or immune injury. For large fistulas rapid surgical repair and drainage is advised, either by reimplantation to the bladder, or native uretero-ureterostomy or uretero-pyelostomy. Small fistulas are occasionally amenable to long-term

stenting with or without a proximal diverting nephrostomy, or bladder catheter. Ureteral stenoses are often amenable to balloon dilation and stenting, but if recurrent require open repair. Urinary retention is more common in recent years as older males with prostatism are transplanted. It is advisable to wait a few months if prostatectomy is needed to ensure healing of the graft. Hydroceles, usually ipsilateral to the transplant and a consequence of spermatic cord transection, may cause discomfort or may enlarge. They are best repaired by hydrocelectomy, although successful aspiration and sclerotherapy has been reported.

3. Wound problems — Wound complications are reported in 5–20% of transplants, and are best prevented since they can cause significant morbidity and take many months to resolve. Since immunosuppression delays wound healing, especially sirolimus and MMF, the use of non absorbable sutures in the fascia and more conservative surgical technique in the obese are warranted. A closed suction pelvic drain is also helpful immediately posttransplant. Early fascial defects or late incisional hernias require operative repair, synthetic mesh or AlloDerm may be required. Suprafascial dehiscence or infection can resolve slowly by secondary intention, which may be hastened by the use of vacuum-assisted closure. Lymphocele formation in the retroperitoneum can develop from disruption of small lymphatic channels in the pelvis or around the kidney. The reported incidence of symptomatic lymphoceles ranges from 6% to 18%, and is influenced by obesity, immunosuppression (mTor inhibitors, steroids), and treatment of rejection. Most are asymptomatic, and resolve spontaneously over several months. Clinical presentation may include abdominal swelling, ipsilateral leg edema, renal dysfunction, or lower urinary voiding symptoms depending upon which pelvic structures are being compressed. Simple aspiration tends to recur; definitive treatments include prolonged tube drainage, sclerotherapy (Povidine iodine, fibrin glue, tetracycline, etc.), or marsupialization and drainage into the peritoneal cavity via laparoscopy or open surgery.

B. MEDICAL COMPLICATIONS

1. Bacterial infections — Renal failure and immunosuppression make recipients more susceptible to infections after the transplant that includes bacterial, viral, fungal, and opportunistic pathogens. It is not surprising that such infections occur more often during the first

6 months when doses of immunosuppression are greatest. It is therefore common practice to prophylax recipients against those infective agents that occur with the greatest frequency. Bacterial urinary tract infections are the most common, and are controlled by the use of daily prophylaxis with oral trimethoprim/sulfa for the first year. This antibiotic is particularly useful since it also provides excellent prophylaxis of Pneumocystis carinii pneumonia, an opportunistic infection that is usually restricted to transplant patients,or others immunocompromised by HIV-AIDS, cancer chemotherapy, etc. Breakthrough infections and transplant pyelonephritis need further workup to identity, obstruction, reflux, foreign body, or stones.

2. Viral infections — One of the most significant advances in transplant practice in the last decades has been the control of viral infections, in particular the Herpes viruses (CMV, EBV, VCZ, and HSV), which caused major morbidity and even mortality in past years. These DNA viruses are characterized by transmission from donor to host resulting in primary infections, as well reactivation of latent virus in the host. Therefore, recipients that have had no prior exposure (serologically negative at transplant) are at the greatest risk for infections. CMV is the most frequently encountered pathogen (10–50 % of recipients), and Donor and Recipient serology (anti-CMV IgG) define risk of infection and treatment strategies. The virus can cause an asymptomatic infection (viral DNA copies in the blood); CMV syndrome with fever and leukopenia; and tissue-invasive disease with the liver, lung, GI tract-colon, and retina often infected. The introduction of the potent nucleoside inhibitors acyclovir, ganciclovir, and valganciclovir has largely controlled these infections. Those who receive organs from CMV-positive donors or have had prior exposure are routinely given 3 months of prophylaxis with oral acyclovir or valganciclovir. Some prefer the use of preemptive therapy, awaiting detection by screening for virus. The use of IV ganciclovir is often coadministered with anti-T-cell antibodies for patients at risk. The BK virus, one of the Polyoma virus family, has been encountered as an infectious agent with increasing frequency in kidney recipients. It is often transferred with the donor kidney, shed in the urine, and can cause inflammation and stricture in the ureter. When advanced it can cause polyoma virus associated nephropathy (PVAN), which results in cellular infiltrates and graft damage. The treatment is immunosuppressive drug reduction, and possibly the use of cidofovir or leflunomide, which have some antiviral activity.

3. Fungal infections — Candida urinary infections or esophagitis occur with some frequency, especially in diabetics. The use of oral fluconazole or Mycelex troche provides prophylaxis the first few months. Systemic fungal infections are uncommon, but sporadic cases of aspergillosis, cryptococcosis, histoplasmosis, mucormycosis, etc. are reported. Invasive fungal infections usually require treatment with Amphotericin B, or its liposomal formulation.

4. Posttransplant diabetes — New onset diabetes after renal transplantation is a growing problem (10–20% of adults) that mimics the features of diabetes type 2. It is a result of both impaired insulin production as well as peripheral insulin resistance, and includes patients that have hyperglycemia responsive to oral agents as well as those that require exogenous insulin. It can be diagnosed up to several years after transplant and is attributed to the use of CNI drugs (tacrolimus > cyclosporine) as well as glucocorticoids. Family history, old age, weight gain, hyperlipidemia, sedentary lifestyle, and viral infections are contributing factors.

5. Posttransplant cancer — Immunosuppression impairs immune surveillance, and not surprisingly is associated with an increased incidence of de novo cancers. Compared to the general population, there is a 20-fold increase for non-Hodgkin's lymphomas (including PTLD), non melanoma skin cancers, and Kaposi's sarcoma; 15-fold for kidney cancers, five-fold for melanoma, leukemia, hepatobiliary tumors, cervical and vulvovaginal tumors; three-fold for testicular and bladder cancers; and two fold for most common tumors, eg,colon, lung, prostate, stomach, esophagus, pancreas, ovary, and breast. Posttransplant lympho-proliferative disorders (PTLD) comprise a spectrum of diseases characterized by lymphoid proliferation ranging from benign lymphoid hyperplasia to high-grade invasive lymphoma. Most PTLD are B-cell lymphomas arising as a result of immune suppression and many of these are associated with EBV infections. PTLD is reported to occur in up to 3% of adults and up to 10% of children after kidney or liver transplantation. Since the rates for most malignancies remain higher after kidney transplantation compared with the general population, cancer should continue to be a major focus of prevention.

Source:

1. Tanagho, McAninch - Smith's General Urology 18th edition

2. Eurotransplant.org

3. EAU Guidelines on Renal Transplantation, 2014

4. Danovitch, Handbook of Kidney Transplantation, 5th Edition

Injuries to the Genitourinary Tract

EMERGENCY DIAGNOSIS & MANAGEMENT

About 10% of all injuries seen in the emergency room involve the genitourinary system to some extent. Many of them are subtle and difficult to define and require great diagnostic expertise. Early diagnosis is essential to prevent serious complications.

Initial assessment should include control of hemorrhage and shock along with resuscitation as required. Resuscitation may require intravenous lines and a urethral catheter in seriously injured patients. In men, before the catheter is inserted, the urethral meatus should be examined carefully for the presence of blood.

The history should include a detailed description of the accident. In cases involving gunshot wounds, the type and caliber of the weapon should be determined, since high-velocity projectiles cause much more extensive damage.

The abdomen and genitalia should be examined for evidence of contusions or subcutaneous hematomas, which might indicate deeper injuries to the retroperitoneum and pelvic structures. Fractures of the lower ribs are often associated with renal injuries, and pelvic fractures often accompany bladder and urethral injuries. Diffuse abdominal tenderness is consistent with perforated bowel, free intraperitoneal blood or urine, or retroperitoneal hematoma. Patients who do not have life-threatening injuries and whose blood pressure is stable can undergo more deliberate radiographic studies. This provides more definitive staging of the injury.

Special Examinations

When genitourinary tract injury is suspected on the basis of the history and physical examination, additional studies are required to establish its extent.

CATHETERIZATION AND ASSESSMENT OF INJURY

Assessment of the injury should be done in an orderly fashion so that accurate and complete information is obtained. This process of defining the extent of injury is termed staging.

1. Catheterization

Blood at the urethral meatus in men indicates urethral injury; catheterization should not be attempted if blood is present, but retrograde urethrography should be done immediately. If no blood is present at the meatus, a urethral catheter can be carefully passed to the bladder to recover urine; microscopic or gross hematuria indicates urinary system injury. If catheterization is traumatic despite the greatest care, the significance of hematuria cannot be determined, and other studies must be done to investigate the possibility of urinary system injury.

2. Computed tomography

Abdominal computed tomography (CT) with contrast media is the best imaging study to detect and stage renal and retroperitoneal injuries. It can define the size and extent of the retroperitoneal hematoma, renal lacerations, urinary extravasation, and renal arterial and venous injuries; additionally, it can detect intra-abdominal injuries (liver, spleen, pancreas, bowel). Spiral CT scanning, now common, is very rapid, but it may not detect urinary extravasation or ureteral and renal pelvic injuries.

3. Retrograde cystography

Filling of the bladder with contrast material is essential to establish whether bladder perforations exist. At least 300mL of contrast medium should be instilled for full vesical distention. A film should be obtained with the bladder filled and a second one after the bladder has emptied itself by gravity drainage. These 2 films establish the degree of bladder injury as well as the size of the surrounding pelvic hematomas.

Cystography with CT is excellent for establishing bladder injury. At the time of scanning, this likewise must be done with retrograde filling of the bladder with 300 mL of contrast media to ensure adequate distention to detect injury.

4. Urethrography

A small (12F) catheter can be inserted into the urethral meatus and 3 mL of water placed in the balloon to hold the catheter in position. After retrograde injection of 20 mL of water-soluble contrast material, the urethra will be clearly outlined on film, and extravasation in the deep bulbar area in case of straddle injury — or free extravasation into the retropubic space in case of prostatomembranous disruption — will be visualized.

5. Arteriography

Arteriography may help define renal parenchymal and renal vascular injuries. It is also useful in the detection of persistent bleeding from pelvic fractures for purposes of embolization with Gelfoam or autologous clot.

6. Intravenous urography

Intravenous urography can be used to detect renal and ureteral injury. This is best done with high-dose bolus injection of contrast media (2.0 mL/kg) followed by appropriate films.

CYSTOSCOPY AND RETROGRADE UROGRAPHY

Cystoscopy and retrograde urography may be useful to detect ureteral injury, but are seldom necessary, since information can be obtained by less invasive techniques.

ABDOMINAL SONOGRAPHY

Abdominal sonography has not been shown to add substantial information during initial evaluation of severe abdominal trauma.

INJURIES TO THE KIDNEY

Renal injuries are the most common injuries of the urinary system. The kidney is well protected by heavy lumbar muscles, vertebral bodies, ribs, and the viscera anteriorly. Fractured ribs and transverse vertebral processes may penetrate the renal parenchyma or vasculature. Most injuries occur from automobile accidents or sporting mishaps, chiefly in men and boys. Kidneys with existing pathologic conditions such as hydronephrosis or malignant tumors are more readily ruptured from mild trauma.

Etiology

Blunt trauma directly to the abdomen, flank, or back is the most common mechanism, accounting for 80–85 % of all renal injuries. Trauma may result from motor vehicle accidents, fights, falls, and contact sports. Vehicle collisions at high speed may result in major renal trauma from rapid deceleration and cause major vascular injury. Gunshot and knife wounds cause most penetrating injuries to the kidney; any such wound in the flank area should be regarded as a cause of renal injury until proved otherwise. Associated abdominal visceral injuries are present in 80% of renal penetrating wounds.

Pathology & Classification

A. EARLY PATHOLOGIC FINDINGS

Lacerations from blunt trauma usually occur in the transverse plane of the kidney. The mechanism of injury is thought to be force transmitted from the center of the impact to the renal parenchyma. In injuries from rapid deceleration, the kidney moves upward or downward, causing sudden stretch on the renal pedicle and sometimes complete or partial avulsion. Acute thrombosis of the renal artery may be caused by an intimal tear from rapid deceleration injuries owing to the sudden stretch.

Pathologic classification of renal injuries is as follows:

Grade 1 (the most common) — Renal contusion or bruising of the renal parenchyma. Microscopic hematuria is common, but gross hematuria can occur rarely.

Grade 2 — Renal parenchymal laceration into the renal cortex. Perirenal hematoma is usually small.

Grade 3 — Renal parenchymal laceration extendingthrough the cortex and into the renal medulla. Bleeding can be significant in the presence of large retroperitoneal hematoma.

Grade 4 — Renal parenchymal laceration extending into the renal collecting system; also, main renal artery thrombosis from blunt trauma, segmental renal vein, or both; or artery injury with contained bleeding.

Grade 5 — Multiple Grade 4 parenchymal lacerations, renal pedicle avulsion, or both; main renal vein or artery injury from penetrating trauma.

B. LATE PATHOLOGIC FINDINGS

1. Urinoma — Deep lacerations that are not repaired may result in persistent urinary extravasation and late complications of a large perinephric renal mass and, eventually, hydronephrosis and abscess formation.

2. Hydronephrosis — Large hematomas in the retroperitoneum and associated urinary extravasation may result in perinephric fibrosis engulfing the ureteropelvic junction, causing hydronephrosis. Follow-up excretory urography is indicated in all cases of major renal trauma.

3. Arteriovenous fistula — Arteriovenous fistulas may occur after penetrating injuries but are not common.

4. Renal vascular hypertension — The blood flow in tissue rendered nonviable by injury is compromised; this results in renal vascular hypertension in less than 1% of cases. Fibrosis from surrounding trauma has also been reported to constrict the renal artery and cause renal hypertension.

Clinical Findings & Indications for Studies

The degree of renal injury does not correspond to the degree of hematuria, since gross hematuria may occur in minor renal trauma and only mild hematuria in major trauma. However, not all adult patients sustaining blunt trauma require full imaging evaluation of the kidney. Patients with gross hematuria or microscopic hematuria with shock (systolic blood pressure <90 mmHg) should undergo radiographic assessment; patients with microscopic hematuria without shock need not. However, should physical examination or associated injuries prompt reasonable suspicion of a renal injury, renal imaging should be undertaken. This is especially true of patients with rapid deceleration trauma, who may have renal injury without the presence of hematuria.

SYMPTOMS

There is usually visible evidence of abdominal trauma. Pain may be localized to one flank area or over the abdomen. Associated injuries such as ruptured abdominal viscera or multiple pelvic fractures also cause acute abdominal pain and may obscure the presence of renal injury. Catheterization usually reveals hematuria. Retroperitoneal bleeding may cause abdominal distention, ileus, and nausea and vomiting.

Initially, shock or signs of a large loss of blood from heavy retroperitoneal bleeding may be noted. Ecchymosis in the flank or upper quadrants of the abdomen is often noted. Lower rib fractures are frequently found. Diffuse abdominal tenderness may be found on palpation; an “acute abdomen” usually indicates free blood in the peritoneal cavity. A palpable mass may represent a large retroperitoneal hematoma or perhaps urinary extravasation. If the retro-peritoneum has been torn, free blood may be noted in the peritoneal cavity but no palpable mass will be evident. The abdomen maybe distended and bowel sounds absent.

LABORATORY FINDINGS

Microscopic or gross hematuria is usually present. The hematocrit may be normal initially, but a drop may be found when serial studies are done. This finding represents persistent retroperitoneal bleeding and development of a large retroperitoneal hematoma. Persistent bleeding may necessitate operation.

STAGING AND X-RAYFINDINGS

Staging of renal injuries allows a systematic approach to these problems. Adequate studies help define the extent of injury and dictate appropriate management. For example, blunt trauma to the abdomen associated with gross hematuria and a normal urogram requires no additional renal studies; however, non visualization of the kidney requires immediate arteriography or CT scan to determine whether renal vascular injury exists.

Staging begins with an abdominal *CT scan*, the most direct and effective means of staging renal injuries. This noninvasive technique clearly defines parenchymal lacerations and urinary extravasation, shows the extent of the retroperitoneal hematoma, identifies nonviable tissue, and outlines injuries to surrounding organs such as the pancreas, spleen, liver, and bowel.

Arteriography defines major arterial and parenchymal injuries when previous studies have not fully done so. Arterial thrombosis and avulsion of the renal pedicle are best diagnosed by arteriography and are likely when the kidney is not visualized on imaging studies. The major causes of non visualization on an excretory urogram are total pedicle avulsion, arterial thrombosis, severe contusion causing vascular spasm, and absence of the kidney (either congenital or from operation).

Differential Diagnosis

Trauma to the abdomen and flank are as is not always associated with renal injury. In such cases, there is no hematuria, and the results of imaging studies are normal.

Complications

EARLY COMPLICATIONS

Hemorrhage is perhaps the most important immediate complication of renal injury. Heavy retroperitoneal bleeding may result in rapid exsanguination. Patients must be observed closely, with careful monitoring of blood pressure and hematocrit. Complete staging must be done early.

The size and expansion of palpable masses must be carefully monitored. Bleeding ceases spontaneously in 80–85% of cases. Persistent retroperitoneal bleeding or heavy gross hematuria may require early operation.

Urinary extravasation from renal fracture may show as an expanding mass (urinoma) in the retroperitoneum. These collections are prone to abscess formation and sepsis. A resolving retroperitoneal hematoma may cause slight fever (38.3°C [101°F]), but higher temperatures suggest infection. A perinephric abscess may form, resulting in abdominal tenderness and flank pain.

LATE COMPLICATIONS

Hypertension, hydronephrosis, arteriovenous fistula, calculus formation, and pyelonephritis are important late complications. Careful monitoring of blood pressure for several months is necessary to watch for hypertension. At 3–6 months, a follow-up excretory urogram or CT scan should be obtained to be certain that perinephric scarring has not caused hydronephrosis or vascular compromise; renal atrophy may occur from vascular compromise and is detected by follow-up urography. Heavy late bleeding may occur 1–4 weeks after injury.

Treatment

EMERGENCY MEASURES

The objectives of early management are prompt treatment of shock and hemorrhage, complete resuscitation, and evaluation of associated injuries.

SURGICAL MEASURES

1. *Blunt injuries* — Minor renal injuries from blunt trauma account for 85% of cases and do not usually require operation. Bleeding stops spontaneously with bed rest and hydration. Cases in which operation is indicated include those associated with persistent retroperitoneal bleeding, urinary extravasation, evidence of nonviable renal parenchyma, and renal pedicle injuries (less than 5% of all renal injuries). Aggressive preoperative staging allows complete definition of injury before operation.

2. *Penetrating injuries* — Penetrating injuries should be surgically explored. A rare exception to this rule is when staging has been complete and only minor parenchymal injury, with no urinary extravasation, is noted. In 80% of cases of penetrating injury, associated organ injury requires operation; thus, renal exploration is only an extension of this procedure.

TREATMENT OF COMPLICATIONS

Retroperitoneal urinoma or perinephric abscess demands prompt surgical drainage. Malignant hypertension requires vascular repair or nephrectomy. Hydronephrosis may require surgical correction or nephrectomy.

Prognosis

With careful follow-up, most renal injuries have an excellent prognosis, with spontaneous healing and return of renal function. Follow-up excretory urography and monitoring of blood pressure ensure detection and appropriate management of late hydronephrosis and hypertension.

INJURIES TO THE URETER

Ureteral injury is rare but may occur, usually during the course of a difficult pelvic surgical procedure or as a result of stab or gunshot wounds. Rapid deceleration accidents may avulse the ureter from the renal pelvis. Endoscopic basket manipulation of ureteral calculi may result in injury.

Etiology

Large pelvic masses (benign or malignant) may displace the ureter laterally and engulf it in reactive fibrosis. This may lead to ureteral injury during dissection, since the organ is anatomically malpositioned. Inflammatory pelvic disorders may involve the ureter in a similar way. Extensive carcinoma of the colon or ovary may invade areas outside this organs and directly involve the ureter; thus, resection of the ureter may be required along with resection of the tumor mass. Devascularization may occur with extensive pelvic lymph node dissections or after radiation therapy to the pelvis for pelvic cancer. In these situations, ureteral fibrosis and subsequent stricture formation may develop along with ureteral fistulas. Endoscopic manipulation of a ureteral calculus may result in ureteral perforation or avulsion.

Pathogenesis & Pathology

The ureter may be inadvertently ligated and cut during difficult pelvic surgery. In such cases, sepsis and severe renal damage usually occur postoperatively. If a partially divided ureter is unrecognized at operation, urinary extravasation and subsequent buildup of a large urinoma will ensue, which usually leads to ureterovaginal or ureterocutaneous fistula formation. Intraperitoneal extravasation of urine can also occur, causing ileus and peritonitis. After partial transection of the ureter, some degree of stenosis and reactive fibrosis develops, with concomitant mild to moderate hydronephrosis.

Clinical Findings

SYMPTOMS

If the ureter has been completely or partially ligated during operation, the postoperative course is usually marked by fever of 38.3°C–38.8°C (101°F–102°F) as well as flank and lower quadrant pain. Such patients often experience paralytic ileus with nausea and vomiting. If ureterovaginal or cutaneous fistula develops, it usually does so within the first 10 postoperative days.

Ureteral injuries from external violence should be suspected in patients who have sustained stab or gunshot wounds to the retroperitoneum. The mid portion of the ureter seems to be the most common site of penetrating injury. There are usually associated vascular and other abdominal visceral injuries.

The acute hydronephrosis of a totally ligated ureter results in severe flank pain and abdominal pain with nausea and vomiting early in the postoperative course and with associated ileus. Signs and symptoms of acute peritonitis may be present if there is urinary extravasation into the peritoneal cavity. Watery discharge from the wound or vagina may be identified as urine by determining the creatinine concentration of a small sample urine that has many times the creatinine concentration found in serum and by intravenous injection of 10mL of indigocarmine, which will appear in the urine as dark blue.

LABORATORY FINDINGS

Ureteral injury from external violence is manifested by microscopic hematuria in 90% of cases. Urinalysis and other laboratory studies are of little use in diagnosis when injury has occurred from other causes.

IMAGING FINDINGS

Diagnosis is by *excretory urography* or delayed abdominal *spiral CT scan*. After injection of contrast material, delayed excretion is noted with hydronephrosis. Partial transaction of the ureter results in more rapid excretion, but persistent hydronephrosis is usually present, and contrast extravasation at the site of injury is noted on delayed films.

In acute injury from external violence, the excretory urogram usually appears normal, with very mild fullness down to the point of extravasation at the ureteral transection.

Retrograde ureterography demonstrates the exact site of obstruction or extravasation.

Ultrasonography outlines hydroureter or urinary extravasation as it develops into a urinoma and is perhaps the best means of ruling out ureteral injury in the early postoperative period.

Differential Diagnosis

Postoperative bowel obstruction and peritonitis may cause symptoms similar to those of acute ureteral obstruction from injury. Fever, “acute abdomen”, and associated nausea and vomiting following difficult pelvic surgery are definite indications for screening sonography or excretory urography to establish whether ureteral injury has occurred. Deep wound infection must be considered postoperatively in patients with fever, ileus, and localized tenderness. The same findings are consistent with urinary extravasation and urinoma formation.

Acute pyelonephritis in the early postoperative period may also result in findings similar to those of ureteral injury. Sonography shows normal results, and urography shows no evidence of obstruction.

Complications

Ureteral injury may be complicated by stricture formation with resulting hydronephrosis in the area of injury. Chronic urinary extravasation from unrecognized injury may lead to formation of a large retroperitoneal urinoma. Pyelonephritis from hydronephrosis and urinary infection may require prompt proximal drainage.

Treatment

Prompt treatment of ureteral injuries is required. The best opportunity for successful repair is in the operating room when the injury occurs. If the injury is not recognized until 7–10 days after the event and no infection, abscess, or other complications exist, immediate reexploration and repair are indicated. Proximal urinary drainage by percutaneous nephrostomy or formal nephrostomy should be considered if the injury is recognized late or if the patient has significant complications that make immediate reconstruction unsatisfactory. The goals of ureteral repair are to achieve complete debridement, a tension-free spatulated anastomosis, watertight closure, ureteral stenting (in selected cases), and retroperitoneal drainage.

A. LOWER URETERAL INJURIES

Injuries to the lower third of the ureter allow several options in management. The procedure of choice is reimplantation into the bladder combined with a psoas-hitch procedure to minimize tension on the ureteral anastomosis. An antireflux procedure should be done when possible. Primary ureteroureterostomy can be used in lower-third injuries when the ureter has been ligated without transection. The ureter is usually long enough for this type of anastomosis. A bladder tube flap can be used when the ureter is shorter.

Transureteroureterostomy may be used in lower-third injuries if extensive urinoma and pelvic infection have developed. This procedure allows anastomosis and reconstruction in an area away from the pathologic processes.

B. MIDURETERAL INJURIES

Midureteral injuries usually result from external violence and are best repaired by primary ureteroureterostomy or transureteroureterostomy.

C. UPPER URETERALINJURIES

Injuries to the upper third of the ureter are best managed by primary ureteroureterostomy. If there is extensive loss of the ureter, autotransplantation of the kidney can be done as well as bowel replacement of the ureter.

Most anastomoses after repair of ureteral injury should be stented. The preferred technique is to insert a silicone internal stent through the anastomosis before closure. These stents have a J memory curve on each end to prevent their migration in the postoperative period. After 3–4 weeks of healing, stents can be endoscopically removed from the bladder. The advantages of internal stenting are maintenance of a straight ureter with a constant caliber during early healing, the presence of a conduit for urine during healing, prevention of urinary extravasation, maintenance of urinary diversion, and easy removal.

Prognosis

The prognosis for ureteral injury is excellent if the diagnosis is made early and prompt corrective surgery is done.

Delay in diagnosis worsens the prognosis because of infection, hydronephrosis, abscess, and fistula formation.

INJURIES TO THE BLADDER

Bladder injuries occur most often from external force and are often associated with pelvic fractures. (About 15% of all pelvic fractures are associated with concomitant bladder or urethral injuries.) Iatrogenic injury may result from gynecologic and other extensive pelvic procedures as well as from hernia repairs and transurethral operations.

Pathogenesis & Pathology

The bony pelvis protects the urinary bladder very well. When the pelvis is fractured by blunt trauma, fragments from the fracture site may perforate the bladder. These perforations usually result in extraperitoneal rupture. If the urine is infected, extraperitoneal bladder perforations may result in deep pelvic abscess and severe pelvic inflammation.

When the bladder is filled to near capacity, a direct blow to the lower abdomen may result in bladder disruption. This type of disruption ordinarily is intraperitoneal. Since the reflection of the pelvic peritoneum covers the dome of the bladder, a linear laceration will allow urine to flow into the abdominal cavity. If the diagnosis is not established immediately and if the urine is sterile, no symptoms maybe noted for several days. If the urine is infected, immediate peritonitis and acute abdomen will develop.

.

Clinical Findings

Pelvic fracture accompanies bladder rupture in 90% of cases. The diagnosis of pelvic fracture can be made initially in the emergency room by lateral compression on the bony pelvis, since the fracture site will show crepitus and be painful to the touch.

SYMPTOMS

There is usually a history of lower abdominal trauma. Blunt injury is the usual cause. Patients ordinarily are unable to urinate, but when spontaneous voiding occurs, gross hematuria is usually present. Most patients complain of pelvic or lower abdominal pain. Heavy bleeding associated with pelvic fracture may result in hemorrhagic shock, usually from venous disruption of pelvic vessels. Evidence of external injury from a gunshot or stab wound in the lower abdomen should make one suspect bladder injury, manifested by marked tenderness of the suprapubic area and lower abdomen. An acute abdomen may occur with intraperitoneal bladder rupture. On rectal examination, landmarks may be indistinct because of a large pelvic hematoma.

LABORATORY FINDINGS

Catheterization usually is required in patients with pelvic trauma but not if bloody urethral discharge is noted. Bloody urethral discharge indicates urethral injury, and a urethrogram is necessary before catheterization. When catheterization is done, gross or, less commonly, microscopic hematuria is usually present. Urine taken from the bladder at the initial catheterization should be cultured to determine whether infection is present.

X-RAY FINDINGS

A *plain abdominal film* generally demonstrates pelvic fractures. There may be haziness over the lower abdomen from blood and urine extravasation. A *CT scan* should be obtained to establish whether kidney and ureteral injuries a represent.

Bladder disruption is shown on *cystography*. With intraperitoneal extravasation, free contrast medium is visualized in the abdomen, highlighting bowel loops.

CT cystography is an excellent method for detecting bladder rupture; however, retrograde filling of the bladder with 300 mL of contrast medium is necessary to distend the bladder completely.

Complications

A pelvic abscess may develop from extraperitoneal bladder rupture; if the urine becomes infected, the pelvic hematoma becomes infected too. Intraperitoneal bladder rupture with extravasation of urine into the abdominal cavity causes delayed peritonitis. Partial incontinence may result from bladder injury when the laceration extends into the bladder neck. Meticulous repair may ensure normal urinary control.

Treatment

EMERGENCY MEASURES

Shock and hemorrhage should be treated.

SURGICAL MEASURES

A lower midline abdominal incision should be made. As the bladder is approached in the midline, a pelvic hematoma, which is usually lateral, should be avoided. Entering the pelvic hematoma can result in increased bleeding from release of tamponade and in infection of the hematoma, with subsequent pelvic abscess. The bladder should be opened in the midline and carefully inspected. After repair, a suprapubic cystostomy tube is usually left in place to ensure complete urinary drainage and control of bleeding.

1. Extraperitoneal bladder rupture — Extraperitoneal bladder rupture can be successfully managed with urethral catheter drainage only. (Typically 10 days will provide adequate healing time.) Large blood clots in the bladder or injuries involving the bladderneck should be managed surgically. As the bladder is opened in the midline, it should be carefully inspected and lacerations closed from within. Extraperitoneal bladder lacerations occasionally extend into the

bladder neck and should be repaired meticulously. Such injuries are best managed with indwelling urethral catheterization and suprapubic diversion.

2. Intraperitoneal rupture — Intraperitoneal bladder ruptures should be repaired via a transperitoneal approach after careful transvesical inspection and closure of any other perforations. The peritoneum must be closed carefully over the area of injury. The bladder is then closed in separate layers. At the time of closure, care should be taken that the suprapubic cystostomy is in the extraperitoneal position.

3. Pelvic fracture — Stable fracture of the pubic rami is usually present. In such cases, the patient can be ambulatory within 4–5 days without damage or difficulty. Unstable pelvic fractures requiring external fixation have a more protracted course.

4. Pelvic hematoma — There may be heavy uncontrolled bleeding from rupture of pelvic vessels even if the hematoma has not been entered at operation. At exploration and bladder repair, packing the pelvis with laparotomy tapes often controls the problem. Embolization of pelvic vessels with Gelfoam or skeletal muscle under angiographic controll is useful in controlling persistent pelvic bleeding.

Prognosis

With appropriate treatment, the prognosis is excellent. The suprapubic cystostomy tube can be removed within 10 days, and the patient can usually void normally. Patients with lacerations extending into the bladder neck area may be temporarily incontinent, but full control is usually regained. At the time of discharge, urine culture should be performed to determine whether catheter-associated infection requires further treatment.

INJURIES TO THE URETHRA

Urethral injuries are uncommon and occur most often in men, usually associated with pelvic fractures or straddle-type falls. They are rare in women. Various parts of the urethra may be lacerated, transected, or contused. Management varies according to the level of injury. The ure-

thra can be separated into 2 broad anatomic divisions: *the posterior urethra*, consisting of the prostatic and membranous portions, and the *anterior urethra*, consisting of the bulbous and pendulous portions.

INJURIES TO THE POSTERIOR URETHRA

Etiology

The membranous urethra passes through the pelvic floor and voluntary urinary sphincter and is the portion of the posterior urethra most likely to be injured. When pelvic fractures occur from blunt trauma, the membranous urethra is sheared from the prostatic apex at the prostatomembranous junction. The urethra can be transected by the same mechanism at the interior surface of the membranous urethra.

Clinical Findings

SYMPTOMS

Patients usually complain of lower abdominal pain and inability to urinate. A history of crushing injury to the pelvis is usually obtained.

SIGNS

Blood at the urethral meatus is the single most important sign of urethral injury. The importance of this finding cannot be overemphasized, because an attempt to pass a urethral catheter may result in infection of the periprostatic and perivesical hematoma and conversion of an incomplete laceration to a complete one. The presence of blood at the external urethral meatus indicates that immediate urethrography is necessary to establish the diagnosis. Suprapubic tenderness and the presence of pelvic fracture are noted on physical examination. A large developing pelvic hematoma may be palpated. Perineal or suprapubic contusions are often noted. Rectal examination may reveal a large pelvic hematoma with the prostate displaced superiorly. Rectal examination can be misleading, however, because a tense pelvic hematoma may resemble

the prostate on palpation. Superior displacement of the prostate does not occur if the puboprostatic ligaments remain intact. Partial disruption of the membranous urethra (currently 10% of cases) is not accompanied by prostatic displacement.

X-RAYFINDINGS

Fractures of the bony pelvis are usually present. A *urethrogram* shows the site of extravasation at the prostatomembranous junction. Ordinarily, there is free extravasation of contrast material into the perivesical space. Incomplete prostatomembranous disruption is seen as minor extravasation, with a portion of contrast material passing into the prostatic urethra and bladder.

INSTRUMENTAL EXAMINATION

The only instrumentation involved should be for urethrography. Catheterization or urethroscopy should not be done, because these procedures pose an increased risk of hematoma, infection, and further damage to partial urethral disruptions.

Differential Diagnosis

Bladder rupture may be associated with posterior urethral injuries in approximately 20% of cases. Cystography cannot be done preoperatively, since a urethral catheter should not be passed. Careful evaluation of the bladder at operation is necessary.

Complications

Stricture, impotence, and incontinence as complications of prostatomembranous disruption are among the most severe and debilitating mishaps that result from trauma to the urinary system. Stricture following primary repair and anastomosis occurs in about 50% of cases. If the preferred suprapubic cystostomy approach with delayed repair is used, the incidence of stricture can be reduced to about 5%.

The incidence of impotence after primary repair is 30–80% (mean, about 50%). This figure can be reduced to 30–35% by suprapubic drainage with delayed urethral reconstruction. Total

urinary incontinence occurs in <2% of patients and typically is associated with severe sacral fracture and S2-4 nerve injury.

Treatment

A. EMERGENCYMEASURES

Shock and hemorrhage should be treated.

B. SURGICALMEASURES

Urethral catheterization should be avoided.

1. Immediate management — Initial management should consist of suprapubic cystostomy to provide urinary drainage. A midline lower abdominal incision should be made, with care being taken to avoid the large pelvic hematoma. The bladder and prostate are usually elevated superiorly by large periprostatic and perivesical hematomas. The bladder often is distended by a large volume of urine accumulated during the period of resuscitation and operative preparation. The urine is often clear and free of blood, but gross hematuria may be present. The bladder should be opened in the midline and carefully inspected for lacerations. If a laceration is present, the bladder should be closed with absorbable suture material and a cystostomy tube inserted for urinary drainage. This approach involves no urethral instrumentation or manipulation. The suprapubic cystostomy is maintained in place for about 3 months. This allows resolution of the pelvic hematoma, and the prostate and bladder will slowly return to their anatomic positions.

Incomplete laceration of the posterior urethra heals spontaneously, and the suprapubic cystostomy can be removed within 2–3 weeks. The cystostomy tube should not be removed before voiding cystourethrography shows that no extravasation persists.

2. Delayed urethral reconstruction — Reconstruction of the urethra after prostatic disruption can be undertaken within 3 months, assuming there is no pelvic abscess or other evidence of persistent pelvic infection. Before reconstruction, a combined cystogram and urethrogram should be done to determine the exact length of the resulting urethral stricture. This stricture usually is 1–2cm long and situated immediately posterior to the pubic bone. The preferred approach is a

single-stage reconstruction of the urethral rupture defect with direct excision of the strictured area and anastomosis of the bulbous urethra directly to the apex of the prostate. A 16F silicone urethral catheter should be left in place along with a suprapubic cystostomy. Catheters are removed within a month, and the patient is then able to void.

3. Immediate urethral realignment — Some surgeons prefer to realign the urethra immediately. Persistent bleeding and surrounding hematoma create technical problems. The incidence of stricture, impotence, and incontinence appears to be higher than with immediate cystostomy and delayed reconstruction.

C. GENERALMEASURES

After delayed reconstruction by a perineal approach, patients are allowed ambulation on the first postoperative day and usually can be discharged within 3 days.

D. TREATMENTOF COMPLICATIONS

Approximately 1 month after the delayed reconstruction, the urethral catheter can be removed and a voiding cystogram obtained through the suprapubic cystostomy tube. If the cystogram shows a patent area of reconstruction free of extravasation, the suprapubic catheter can be removed; if there is extravasation or stricture, suprapubic cystostomy should be maintained. A follow-up urethrogram should be obtained within 2 months to watch for stricture development.

Stricture, if present (<5%), is usually very short, and urethrotomy under direct vision offers easy and rapid cure. The patient may be impotent for several months after delayed repair. Impotence is permanent in about 10% of patients. Incontinence after posterior urethral rupture and delayed repair is rare (<2%) and is usually related to the extent of injury rather than to the repair.

Prognosis

If complications can be avoided, the prognosis is excellent. Urinary infections ultimately resolve with appropriate management.

INJURIES TO THE ANTERIOR URETHRA

Etiology

The anterior urethra is the portion distal to the urogenital diaphragm. Straddle injury may cause laceration or contusion of the urethra. Self-instrumentation or iatrogenic instrumentation may cause partial disruption. Contusion of the urethra is a sign of crush injury without urethral disruption. Perineal hematoma usually resolves without complications.

LACERATION

A severe straddle injury may result in laceration of part of the urethral wall, allowing extravasation of urine. If the extravasation is unrecognized, it may extend into the scrotum, along the penile shaft, and up to the abdominal wall. It is limited only by Colles' fascia and often results in sepsis, infection, and serious morbidity.

Clinical Findings

SYMPTOMS

There is usually a history of a fall, and in some cases a history of instrumentation. Bleeding from the urethra is usually present. There is local pain into the perineum and sometimes massive perineal hematoma. If voiding has occurred and extravasation is noted, sudden swelling in the area will be present. If diagnosis has been delayed, sepsis and severe infection may be present.

The perineum is very tender; a mass may be found, as may blood at the urethral meatus. Rectal examination reveals a normal prostate. The patient usually has a desire to void, but voiding should not be allowed until assessment of the urethra is complete. No attempt should be made to pass a urethral catheter, but if the patient's bladder is overdistended, percutaneous suprapubic cystostomy can be done as a temporary procedure.

When presentation of such injuries is delayed, there is massive urinary extravasation and infection in the perineum and the scrotum. The lower abdominal wall may also be involved. The skin is usually swollen and discolored.

LABORATORY FINDINGS

Blood loss is not usually excessive, particularly if secondary injury has occurred. The white count may be elevated with infection.

X-RAYFINDINGS

A urethrogram demonstrates extravasation and the location of injury. A contused urethra shows no evidence of extravasation.

Complications

Heavy bleeding from the corpus spongiosum injury may occur in the perineum as well as through the urethral meatus. Pressure applied to the perineum over the site of the injury usually controls bleeding. If hemorrhage cannot be controlled, immediate operation is required.

The complications of urinary extravasation are chiefly sepsis and infection. Aggressive debridement and drainage are required if there is infection. Stricture at the site of injury is a common complication, but surgical reconstruction may not be required unless the stricture significantly reduces urinary flow rates.

Treatment

GENERAL MEASURES

Major blood loss usually does not occur from straddle injury. If heavy bleeding does occur, local pressure for control, followed by resuscitation, is required.

SPECIFIC MEASURES

1. Urethral contusion — The patient with urethral contusion shows no evidence of extravasation, and the urethra remains intact. After urethrography, the patient is allowed to void; and if the voiding occurs normally, without pain or bleeding, no additional treatment is necessary. If bleeding persists, urethral catheter drainage can be done.

2. Urethral lacerations — Instrumentation of the urethra following urethrography should be avoided. A small midline incision in the suprapubic area readily exposes the dome of the bladder so that a suprapubic cystostomy tube can be inserted, allowing complete urinary diversion while the urethral laceration heals. Percutaneous cystostomy may also be used in such injuries. If only minor extravasation is noted on the urethrogram, a voiding study can be performed within 7 days after suprapubic catheter drainage to search for extravasation. In more extensive injuries, one should wait 2–3 weeks before doing a voiding study through the suprapubic catheter. Healing at the site of injury may result in stricture formation. Most of these strictures are not severe and do not require surgical reconstruction. The suprapubic cystostomy catheter may be removed if no extravasation is documented. Follow-up with documentation of urinary flow rates will show whether there is urethral obstruction from stricture.

3. Urethral laceration with extensive urinary extravasation — After major laceration, urinary extravasation may involve the perineum, scrotum, and lower abdomen. Drainage of these areas is indicated. Suprapubic cystostomy for urinary diversion is required. Infection and abscess formation are common and require antibiotic therapy.

4. Immediate repair — Immediate repair of urethral lacerations can be performed, but the procedure is difficult and the incidence of associated stricture is high.

TREATMENT OF COMPLICATIONS

Strictures at the site of injury may be extensive and require delayed reconstruction.

Prognosis

Urethral stricture is a major complication but in most cases does not require surgical reconstruction. If, when stricture resolves, urinary flow rates are poor and urinary infection and urethral fistula are present, reconstruction is required.

INJURIES TO THE PENIS

Disruption of the tunica albuginea of the penis (penile fracture) can occur during sexual intercourse. At presentation, the patient has penile pain and hematoma. This injury should be surgically corrected.

Gangrene and urethral injury may be caused by obstructing rings placed around the base of the penis. These objects must be removed without causing further damage. Penile amputation is seen occasionally, and in a few patients, the penis can be surgically replaced successfully by microsurgical techniques.

Total avulsion of the penile skin occurs from machinery injuries. Immediate debridement and skin grafting are usually successful in salvage. Injuries to the penis should suggest possible urethral damage, which should be investigated by urethrography.

INJURIES TO THE SCROTUM

Superficial lacerations of the scrotum may be debrided and closed primarily. Blunt trauma may cause local hematoma and ecchymosis, but these injuries resolve without difficulty. One must be certain that testicular rupture has not occurred.

Total avulsion of the scrotal skin may be caused by machinery accidents or other major trauma. The testes and spermatic cords are usually intact. It is important to provide coverage for these structures: this is best done by immediate surgical debridement and by placing the testes and spermatic cords in the subcutaneous tissues of the upper thighs. Later reconstruction of the scrotum can be done with a skin graft or thigh flap.

INJURIES TO THE TESTIS

Blunt trauma to the testis causes severe pain and, often, nausea and vomiting. Lower abdominal tenderness may be present. A hematoma may surround the testis and make delineation of its

margin difficult. Ultrasonography can be used as an aid to better define the organ. If rupture has occurred, the sonogram will delineate the injury, which should be surgically repaired.

Source:

1. Tanagho, McAninch - Smith's General Urology 18th edition

2. Wessells, McAninch - Urological Emergencies, 2005

3. EAU Guidelines Urological Trauma, 2016