CHAPTER

25 Complicated Urinary Tract Infections

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Complicated infections of the genitourinary (GU) tract refer to those infections that occur in the presence of anatomic or functional abnormalities in the kidney, bladder, or collecting systems (including vesicoureteral reflux and neurogenic bladders in patients with spinal cord injury); obstruction to normal urine flow (including renal, ureteric and bladder calculi, and prostatic hypertrophy); urinary tract catheterization or instrumentation; cystic renal disease; specific diseases such as diabetes mellitus; and abnormalities in host defense mechanisms and those infections that follow surgery or renal transplantation (Table 25.1). In addition, infections that are caused by organisms that resist antimicrobial therapy (such as multidrug-resistant gram-negative rods and enterococci) or that might otherwise be difficult to eradicate may be considered in this category. Aerobic or anaerobic bacteria, mycobacteria, fungi, parasites, and even viruses may cause complicated infections.

Other conditions associated with complicated urinary infections include prostatic, kidney, or perinephric abscesses; pyonephrosis; emphysematous pyelonephritis and cystitis; malakoplakia and xanthogranulomatous pyelonephritis; intramural vesicle abscesses; pyelonephritis with bacteremia and sepsis; and tuberculosis. Some of these conditions are discussed in other chapters. Complicated urinary infections occur either in the upper or lower urinary tract and may be acute or chronic. Not included in this category are asymptomatic bacteriuria, urethritis, acute cystitis, acute pyelonephritis, or recurrent upper or lower urinary tract infections (UTIs) occurring in the presence of a normal urinary system.

ANATOMIC OR STRUCTURAL RISK FACTORS

Obstructive Uropathy

Obstructive uropathy includes: calculi at any level of the urinary tract; prostatic hypertrophy; cancer of the prostate, bladder, or uterus; external compression by uterine or other tumors; neurogenic bladder; and congenital abnormalities. Any of these conditions may be associated with a complicated UTI. An obstruction above the bladder can lead to renal pelvic dilatation and hydronephrosis with subsequent pressure atrophy of renal cortical tissue. When an infection does occur in the setting of partial or complete obstruction, the clearance of an infection is more difficult because drainage may be limited, antibiotic penetration might decrease, and host responses may be impaired.

Obstruction of the urinary tract may be acute or chronic, unilateral or bilateral, and complete or incomplete. Acute obstruction of the upper urinary tract may be associated with retroperitoneal or flank pain, especially if calculi are present. Obstruction at the bladder level increases the risk of infection by decreasing the effect of micturition on reducing bacterial inocula as well as allowing for the multiplication of bacteria to the degree that mucosal antibacterial and other host factors are overwhelmed or inactivated. An obstruction at higher levels of the urinary tract may predispose the patient to infection because dilatation and pressure necrosis may decrease defense mechanisms in the kidney and may allow disseminating hematogenous bacteria to alight and form a nidus of infection in the renal cortex or medulla. Also, once the normal architecture of the urinary tract has been damaged, whether as a result of reflux or obstruction, bacteria that lack the virulence factors necessary to cause renal infection in the absence of structural lesions may be responsible for serious upper tract infection once introduced into the kidney.

The treatment of urinary infections in the face of obstructive uropathy or stone disease usually requires antibiotic therapy for a longer duration than that for uncomplicated infections; treatment may be required for up to 6 weeks. Obviously, correction of the obstruction and removal of calculi are important adjunctive measures. In general, a 6-week course of a bactericidal antibiotic that achieves adequate concentration in renal tissue and bladder urine is recommended. Depending on the organism and susceptibility testing results, intravenous or oral therapy can be used; for example, a fluoroquinolone or a β-lactam antibiotic. Susceptibility testing is particularly important given the increased frequency of antibiotic-resistant bacteria in complicated urinary tract infections.[1] Special consideration is needed in the

25.1 Complicated Infections of the Urinary Tract

Anatomic or Structural Risk Factors

- Obstructive uropathy—stones, strictures, tumors
  - Prostate associated (see Chapter 23)
- Instrumentation—catheter associated and nosocomial
- Renal cystic disease
- Ureteral stents and surgical urinary diversions
  - Ileal loop constructions
- Other anatomic risk factors
  - Vesicoureteral reflux
  - Urachal remnants

Functional Risk Factors

- Diabetes mellitus
- Renal transplantation
- Spinal cord injury and neurologic dysfunction
- Neutropenia
- HIV

Miscellaneous Complicated Infections

- Pyonephrosis
- Emphysematous pyelonephritis and cystitis
- Malakoplakia and xanthogranulomatous pyelonephritis
- Intramural vesicle abscess
- Urosepsis
- Tuberculosis (see Chapter 27)
- Infections caused by atypical or resistant organisms
  (e.g., vancomycin-resistant enterococci, ESBL-producing gram-negative rods, anaerobes)

ESBL, extended spectrum beta-lactamase.

face of staghorn calculi, which often form in the presence of urease-producing organisms such as Proteus spp. Once the organism has been eradicated with a long course of antibiotics, "prophylactic" or "suppressive" therapy can be given with low-dose trimethoprim-sulfamethoxazole, daily or every other day, or with a combination of trimethoprim and a methenamine compound. Nephrolithiasis is considered in more detail in Chapter 20.

Catheterization and Instrumentation

The distal third of the urethra is normally colonized with perineal and skin flora. Instrumentation for any reason may introduce these organisms into the bladder. In the presence of an indwelling catheter, bacteria can ascend from the periurethral area along the mucous sheath that develops between the urethral mucosa and the latex rubber catheter.[2] Although several techniques have been introduced to prevent urinary infection in chronically catheterized patients, such as closed sterile drainage, continuous irrigation through a three-way catheter with antibiotic or acetic acid, and systemic antibiotic prophylaxis, all patients with prolonged urinary catheter drainage ultimately become colonized with high counts of bacteria (from 2 to about 21 days).

Catheter-associated bacteriuria and catheter-associated urinary tract infections (CA-UTIs) are the most common infection acquired in hospitals and long-term care facilities (LTCF);[3] elderly patients are at greatest risk. Over 40% of nosocomial infections originate in the urinary tract and Escherichia coli is responsible for most of these infections, followed by Enterococcus spp., Pseudomonas aeruginosa, and Candida spp.[3–5] Bacteremia, an important sequela of complicated UTIs, develops in about 4% of patients with indwelling bladder catheter-associated urinary infections, and case-fatality rates of 13% to 30% have been reported for these bacteremic nosocomial urinary infections.[3,5–6]

Catheter-associated nosocomial UTIs (CA-UTI) have been described in a study of 1,497 patients. These infections were more frequent in women (23.2%) than men (8.9%). They were unimicrobial in 94% and polymicrobial (primarily with enterococci and gram-negative bacilli) in 6%. The distribution of single isolates in these patients included gram-negative bacilli in 34%, enterococci or staphylococci in 27%, and Candida spp. in 27%. Patients with CA-UTIs only rarely have symptoms (<10%) in the face of infections and pyuria, and they may not have peripheral leukocytosis.[7,8] Catheters left in place without bona fide medical necessity often contribute to nosocomial infections and are accompanied by an increase in associated antibiotic costs.[9]

Environmental factors may relate to the nosocomial acquisition of bacteriuria in catheterized patients. Prevalent bacteria in the hospital colonize patients, or the patient's endogenous flora may enter the urinary collecting system or drainage bag. Within 24 to 48 hours they may be found in the bladder, and they increase to high colony counts over the subsequent 48 hours.[10,11] Bacteria may attach to the luminal surface of the catheter in association with the production of a mucoid biofilm, and this may predispose the patient to urinary infection or catheter blockage and obstruction.[7,10]

Urea splitting bacteria may lead to mucosal encrustations and encrusted cystitis and pyelitis. Corynebacterium group D_2 also have been implicated.[12] There is often a history of a prior urologic procedure or chronic illness, including immune compromise or renal transplantation. Patients may describe symptoms of cystitis, dysuria, gross hematuria, passage of encrusted debris, often with complaints of an ammonia odor to the urine. Failure to diagnose this condition can lead to renal impairment or ureteric obstruction and loss of renal graft as a result of infection, renal abscess, or obstructive uropathy. Treatment consists of antibiotics. The glycopeptides vancomycin and teicoplanin have in vitro activity against Corynebacterium group D_2, which are frequently resistant to fluoroquinolone antibiotics (>50%).

Additional treatment includes acidification of urine as well as chemolysis and the removal of infected calcified plaques that contain the organisms.[12]

Some caution is warranted in interpreting the results of cultures of material obtained from urinary collection devices. Several populations of bacteria may grow within the catheter and include planktonic bacteria in the urine and surface bacteria associated with the bacterial biofilm.[13] Bacteria may be cultured from catheter lumen encrustations when bladder urine might be sterile.[14] Because bladder urine is normally sterile, Garibaldi and associates[15] suggested that the presence of 100 or more organisms per milliliter should be considered as evidence of a positive urine culture in a catheterized patient. These authors demonstrated that breaks in the catheter-collecting system junction were associated with an early acquisition of bacteriuria. Current guidelines from the Infectious Diseases Society of America (IDSA) suggest that infection is likely in the presence of compatible signs and symptoms and an indwelling catheter if the bacterial counts of one or more organisms are equal to or greater than 10^3 CFU per milliliter.[3]

Condom catheters are the usual alternatives to indwelling bladder catheters in incontinent male patients without obstructive uropathy. Although associated with fewer infectious complications, at least one outbreak implicated these devices in 64 geriatric patients, 40 (63%) of whom had asymptomatic infections, frequently with mechanical obstruction of urine flow including kinking of the outlet, or blockage of flow by adhesive devices with associated penile cyanosis and ulceration. These problems may lead to urinary stasis, bacteriuria, and bladder wall distention, all of which may predispose a patient to complicated urinary infections.[16]

Treatment of catheter-associated urinary infections depends on the clinical setting. In general, asymptomatic bacteriuria in catheterized patients is not treated. In patients with catheters in place for the long term, there is some risk of dissemination of bladder bacteriuria to the blood during manipulation of the urinary tract as during catheter changes (generally done to minimize concretions and obstruction). Antimicrobial agents have not been shown to prevent catheter associated UTIs in persons with long-term indwelling urethral catheters.[3] Preventive strategies that avoid antibiotics are needed for these patients. We occasionally advocate treating the colonizing bacteria 8 to 24 hours prior to the catheter change, with a single dose of a bactericidal antibiotic based on susceptibility testing of the organisms (e.g., a quinolone or an aminoglycoside). This topic is extensively reviewed in the new IDSA guidelines,[3] and they do not support antibiotics at catheter replacement.

Bacteriuria

Interventional attempts to decrease the incidence of nosocomial UTIs using a silver-alloy, hydrogel-coated latex urinary catheter have been compared with standard silicone-coated latex catheters.[17] In older studies, silver-coated catheters significantly reduced the rates of bacteriuria in male surgical patients not receiving antibiotics.[18] In the more recent study,[17] silver-coated catheters were associated with a 32% decrease in the infection risk in male patients. Infection rates in females were similar in both catheter groups. In addition to a decrease in nosocomial infection rates, significant savings on hospitalization and other infection-related costs were described. Another study estimated that economic consequences of nosocomial symptomatic UTIs can reach over US$650 and catheter-related bacteriuria over US$2,800 per incident.[19] A study by Rupp et al.[20] demonstrated additional cost savings with the silver-alloy hydrogen-coated urinary catheters and also showed a decline in nosocomial UTIs. No evidence of silver-resistant urinary pathogens was found.

Symptomatic urinary infections or urosepsis in the presence of an indwelling catheter is best treated with rapidly bactericidal antibiotics such as an aminoglycoside, a fluoroquinolone, or a β-lactam-aminoglycoside combination based on antimicrobial susceptibility testing.[1] Bacteremia is usually easily cleared, but eradication of the urinary infecting organism may be difficult in the continued presence of the catheter. Guidelines for the prevention and management of catheter-related urinary infections have been updated recently.[3]

Renal Cysts (Including Polycystic Renal Disease)

Complicated infections within or associated with isolated renal cysts, autosomal dominant polycystic renal disease (ADPKD), or acquired renal cystic disease (three or more renal cysts or cystic involvement of >25% of renal mass in the absence of autosomal dominant polycystic kidney disease) remain important diagnostic and therapeutic challenges.[21]

Patients with polycystic kidney disease may develop typical infections of the urinary bladder and ascending pyelonephritis with renal parenchymal involvement as well as infection within the renal cysts themselves.[22] The presence of polycystic kidney disease is associated with a 50% to 70% lifetime risk of some form of UTI.[23] In an autopsy study of 23 patients with polycystic kidney disease, 13 (56%) had findings consistent with pyelonephritis.[24] It may be difficult to implicate infection as a cause of hematuria or flank pain in patients with cystic abnormalities of the kidney because these symptoms may be present in the absence of infection.[25] Also, pyuria (≥10 leukocytes/high-power field) may be present in more than 40% of patients with polycystic kidney disease, with or without other symptoms suggestive of urinary tract infection; however, infection is documented in only about 10% of these patients.[26] Findings suggestive of a UTI in the presence of cystic renal disease include positive blood cultures, leukocytosis, fever, and lower GU tract symptoms such as dysuria. Negative urine cultures do not exclude infection of a renal cyst.

In a classic review of renal infections in patients with polycystic kidney disease, Sklar and associates[25] described

four types of infections according to anatomic involvement: (1) localized infected cyst (pyocyst), (2) pyonephrosis (intrarenal abscess associated with ureteral obstruction), (3) acute bacterial interstitial nephritis, and (4) perinephric abscess. Clinical findings may vary with the anatomic location of bacterial infections in these patients.

The diagnosis of complicated UTIs in patients with renal cystic disease is usually based on the results of clinical examination, laboratory testing, and diagnostic imaging. Radiologic evaluation with plain radiography, ultrasound, computed tomography (CT), and gallium imaging has been used to determine the presence and location of infection.[25] Gallium imaging may show uptake within the kidney, but it does not provide specific information to determine whether an abscess or an infected cyst is present. CT may be necessary to define pyocysts but CT scans are not optimal in distinguishing infected from noninfected cysts. Plain radiography may be useful if calculi are contributing to the clinical presentation. Renal ultrasonography also may identify calculi and can differentiate hydronephrosis from pyonephrosis and perinephric abscess. Recent studies suggest that positron emission tomography (PET) scanning and diffusion-weighted magnetic resonance imaging (MRI) might be useful in differentiating infected from noninfected cysts.[21,27] The percutaneous drainage of infected cysts in adult polycystic kidney disease has been described, as has laparoscopic cyst decortication using transperitoneal or retroperitoneal access.[28,29]

When cysts are infected, the Enterobacteriaceae (especially E. coli, Klebsiella spp., and Proteus spp.) and P. aeruginosa are most frequently implicated, with Staphylococcus aureus, Salmonella spp., Streptococcus spp., Corynebacterium spp., and others isolated less frequently.[21,30] A gas producing Clostridium perfringens infection in a renal cyst has been reported in a patient with ADPKD.[31]

Attempts should be made to isolate the infecting organism from the blood, urine, or cyst drainage. Appropriate treatment of infections in patients with polycystic kidney disease depends on the use of antibiotics that are able to concentrate within the infected cysts in addition to providing bactericidal activity against the infecting organism. Aminoglycosides, penicillins, and cephalosporins have relatively poor penetration into renal cysts, although pH, cyst physiology, and histology may affect the diffusion.[32] These antibiotics are relatively lipophobic and do not diffuse across cyst epithelial layers. Lipophilic agents such as clindamycin, chloramphenicol, macrolides, metronidazole, and trimethoprim are able to penetrate and accumulate within cysts, but they may or may not be active against the infecting organisms.[33] Fluoroquinolone antibiotics such as ciprofloxacin accumulate in cystic fluid, and they have been used successfully to treat infected renal cysts.[34,35] Because most of the causative organisms in infected cysts are facultative gram-negative bacilli with presumed fluoroquinolone susceptibility, these agents may still be quite useful clinically. Oral therapy is acceptable unless patients are septic. Infection in multiple cysts has been associated with sepsis and may require surgical intervention (nephrectomy) in rare cases.[36] Intravenous therapy should be used in bacteremic patients and in patients with decreased gastrointestinal (GI) quinolone absorption (e.g., antacid use). Antibiotic choice should be based on pharmacology and antibiotic susceptibility testing given the increased incidence of antibiotic resistance among gram-negative bacilli.[1]

Urinary Diversion

Ureteral Stents

Ureteral stents are placed in the treatment of hydronephrosis and obstruction caused by nephrolithiasis or malignancies, and as adjuncts to lithotripsy and open surgical procedures on the urinary tract. These stents are made of synthetic polymers and are either indwelling (self-retained in place between the renal pelvis and the bladder) or external.

Complications of indwelling ureteral stents include fever, infection, gross or microscopic hematuria, biofilm development and stent rupture, catheter migration, encrustation and bladder stone formation, and vesicoureteral reflux.[37] Infection in the presence of stent obstruction is problematic and difficult to eradicate. Also, it is often difficult to differentiate symptoms caused by an infection from those associated with the presence of a stent, which include hematuria, dysuria, increased urinary frequency, nocturia, and loin pain. Bacterial colonization of stents is common and Enterobacteriaceae, staphylococci, streptococci, and Pseudomonas aeruginosa are most frequent.[38,39]

Positive urine cultures with supporting clinical evidence for urinary infection should stimulate prompt antibiotic treatment to eradicate the infecting pathogens. Ureteral stents that develop biofilm formation and encrustations treated in vivo with oral ciprofloxacin or ofloxacin absorb these antibiotics.[40] Attempts to determine the presence of bacterial stent colonization are not reliable. Despite negative urine cultures, stents may be colonized with bacteria or fungi. Double-J ureteral stents can become colonized with gram-negative bacteria within 2 weeks of placement. Risk factors for stent colonization and urinary infection include diabetes mellitus, chronic renal failure, and pregnancy.[39] Silicone ureteral stents compared with low surface energy stents and hydrogel-coated stents demonstrated less encrustation in the presence of urease-producing bacteria (Proteus mirabilis). These results may indicate a reduced risk of encrustation and P. mirabilis infection with this stent,[41] but biofilm formation and subsequent colonization and encrustation remain important challenges.[37] Triclosan-eluting stents might result in a reduction in symptomatic infections and antibiotic use, but their ultimate role needs more study.[42] The presence of bacteremia and other signs of systemic infection suggest infection in the face of possible occlusion or obstruction of the stent, and stent removal is essential.

Surgical Urinary Diversion

Urinary diversions are performed to reroute urine in patients with obstructive uropathy from many causes—urinary bladder carcinoma or prostatic or gynecologic malignancies—and in

patients with congenital abnormalities, neurologic disorders, and pelvic trauma. Although intermittent catheterization may be preferable in some patients with neurogenic bladder dysfunction (e.g., multiple sclerosis, paraplegia), the creation of a ureteroileal conduit is a popular alternative to achieve control of urine excretion. This procedure does not carry the associated metabolic and electrolyte complications seen with jejunal bypass procedures. The surgical construction of an ileal loop conduit is associated with few serious complications and a low mortality rate.

Infectious complications have been well described in pediatric and adult populations, and an increased incidence of infections has been noted when the ureteric component becomes obstructed; pyelonephritis may result. Renal calculi are encountered frequently after urinary diversion and are often caused by urea-splitting organisms such as P. mirabilis and Proteus morganii. The urease produced by these organisms splits urea to form an alkaline pH, and the solubility product constant for calcium and phosphate is exceeded with the resultant precipitation of crystals, which form the nidus for renal stones.[43,44] Newer diversion procedures have been introduced (such as orthotopic urinary diversion or the neobladder) and also carry a risk of urinary infection.[45]

Recommendations for the management of these patients include aggressive control of the infection using bactericidal drugs active against urea-splitting organisms and acidification of the urine or avoidance of alkaline urinary pH, which encourages stone formation. The detection of urinary infection in these patients is difficult because the ileal loops are almost always colonized. Asymptomatic bacteriuria in the presence of a ureteroileal conduit should not be treated and prophylactic antibiotics are not recommended; this is less clear with orthotopic diversions.[45] However, positive urine cultures associated with physical findings of fever, chills, and flank pain should prompt the initiation of appropriate bactericidal antibiotics directed against gram-negative enteric rods including Proteus spp. Aminoglycosides, fluoroquinolones, third- or fourth-generation cephalosporins, carbapenems, and penicillin-β-lactamase inhibitor combinations (e.g., ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate) may be useful in this setting. When susceptibilities are known, specific therapy can be instituted. Septic complications often lead to failure of ileal diversions.[46]

Other Anatomic Risk Factors

Vesicoureteral Reflux

Conditions that allow for the reflux of urine from the bladder to the ureters and subsequently the kidneys are associated with increased frequencies of acute and chronic pyelonephritis. Various degrees of vesicoureteral reflux may occur congenitally, and once the bladder urine is infected, an upper tract infection is facilitated by the retrograde flow. In this setting, organisms that cause infection may be relatively free of virulence factors such as hemolysins, pili, and other adhesions (Chapter 55). Vesicoureteral reflux is associated with progressive renal scarring in children, even in the absence of infected urine, and these patients have an increased risk of renal damage and even renal failure when infection does occur.[47]

In a study of the etiologies of renal scarring, Huland and Busch[48] evaluated 213 patients with recurrent UTIs. Forty-two patients (26%) were found to have pyelonephritic scarring and renal insufficiency. Twenty-eight (67%) of these patients had urinary infections in the presence of vesicoureteral reflux. Young children under 4 years of age with intrarenal reflux have a well demonstrated risk of renal scarring.[47]

The approach to the treatment of patients with documented vesicoureteral reflux and recurrent UTIs includes antibiotic management plus surgical reconstruction (antireflux operation). Hendren[49] reported that more than 70% of very young children no longer had urinary infections after the surgical procedure. Long-term antibiotic chemoprophylaxis to prevent recurring UTIs has been studied in addition to surgical reconstruction. However, a recent review has questioned the use of this approach. A Cochrane Database review of several published randomized placebo-controlled trials showed a benefit of long-term antibiotics (10 to 52 weeks) to reduce the frequency of symptomatic UTI recurrences. However, this benefit was small and is associated with a risk of antimicrobial resistance.[50]

Two recent publications highlight ongoing controversies in the management of vesicoureteral reflux in children given newly developed endoscopic procedures in the face of the traditional approach of continuous antibiotic prophylaxis.[51,52] The optimal approach to the prevention of renal scarring remains under active investigation.[53]

Infected Urachal Remnants/Cysts

Acute and recurrent UTIs in the presence of abnormalities of urachal development with patent urachal remnants may be difficult to diagnose. Four primary developmental defects exist and present with varying signs and symptoms: patent urachus, umbilical urachal sinus, vesicourachal diverticulum, and urachal cyst.[54] Umbilical urachal sinuses and urachal cysts are only rarely infected and many urachal cysts are found incidentally during surgery or radiographic studies. Although most patent urachal remnants in adults are undetected and asymptomatic, umbilical urachal sinuses occasionally may be infected and present with purulent umbilical drainage or periumbilical erythema. These infections may present as infraumbilical abdominal wall abscesses or with contiguous involvement of the peritoneal cavity with an enteric fistula. Adult and pediatric cases have been reviewed.[54–56]

A vesicourachal diverticula may present with recurrent urinary infections, and urethral discharge, pneumaturia, and a suprapubic mass also may be found. Imaging studies may help make the diagnosis, but often cystoscopy may be necessary, especially if the diverticulum is associated with malignant transformation of the remnant. The organisms that infect the vesicourachal diverticula include E. coli and other Enterobacteriaceae, S. aureus, Enterococcus spp., and Actinomyces spp.[54,57]

FUNCTIONAL RISK FACTORS

Diabetes Mellitus

Many factors that predispose the diabetic patient to infections in the urinary tract have been described. Diabetes mellitus is putatively associated with an increased risk of these infections as a result of poorly controlled plasma glucose concentrations, which in turn may impair granulocyte function and cell-mediated immunity. Also, the neurologic dysfunction associated with diabetic neuropathy may result in a neurogenic bladder with incomplete bladder emptying, urinary stasis, and retention. The increased likelihood of urethral instrumentation may predispose these patients to infection, as may diabetic microangiopathy, which can contribute to local ischemia and impaired host defenses.[58,59]

Table 25.2 lists the manifestations of UTIs in patients with diabetes mellitus. Asymptomatic bacteriuria has been described as occurring two to four times more frequently in diabetic women[59,60] and as being more prevalent in diabetic women than men.[61] Although the treatment of asymptomatic bacteriuria in diabetic women reduced the duration of long-term bacteriuria, recolonization occurred after most treatment regimens.[62] A recent study in type 1 diabetic women suggested that sexual activity is more likely to be a risk factor for cystitis and pyelonephritis than diabetes control or complications.[63] In one recent small series, the distribution of responsible pathogens was similar among diabetic and nondiabetic patients, as was the frequency of infection with antibiotic-resistant organisms.[64] Bacteriuria in diabetic patients may be associated with a disproportionate risk of infection in the upper urinary tract and kidneys, and one study reported that upper tract infection could be documented in 79% of diabetic women with asymptomatic bacteriuria.[60] Other renal parenchymal complications of UTIs in diabetic patients include pyelonephritis, emphysematous pyelonephritis, papillary necrosis, and perinephric abscesses; these conditions should be considered in the evaluation of nonresponse to appropriate antibiotic therapy for urinary infections in diabetic patients.

Diabetic patients with urinary infections are more likely to be bacteremic or uroseptic than are nondiabetic patients.[65] These patients are also more likely to develop acute pyelonephritis at a fivefold greater risk than nondiabetic patients.[66] Diabetic patients with serious systemic signs of urinary infections should be studied with abdominal radiography to detect renal emphysematous pyelonephritis. Ultrasound or CT scans should be performed if an obstruction or an abscess is suspected. The urinary tract is implicated as the source of bacteremia more frequently in diabetic than in nondiabetic patients.[65] Postmenopausal women with diabetes are at a higher risk of a UTI and this is related to the duration of diabetes and insulin dependence.[67] Type 2 diabetic women with histories of UTIs (especially upper UTIs) are at increased risk for renal scarring and damage, as demonstrated by renal cortex scans.[68] Most of the bacteria responsible for urosepsis in diabetics are gram-negative rods, with E. coli and Klebsiella spp. accounting for about 70%. Notably, Klebsiella spp. are isolated frequently in diabetic patients with bacteremic urinary infections, and a large proportion of these patients have indwelling urinary bladder catheters.

In diabetic patients taking oral hypoglycemic agents, trimethoprim-sulfamethoxazole may lead to further hypoglycemia. No such potentiation is seen with most fluoroquinolone antibiotics, but hypoglycemia has been reported with gatifloxacin.[69] Invasive staphylococci also can cause complicated infections that might or might not result in abscess formation. Given the current high frequency of methicillin-resistant Staphylococcus aureus (MRSA), the treatment for staphylococcal urinary infections should begin with vancomycin, and can be modified based on susceptibility testing. Intravenous antibiotics should be administered for the first 2 to 4 days in complicated infections while monitoring for decreasing symptoms and fever. Oral step-down treatment should be continued for 14 days or longer in the presence of complicated infections.

Opal and associates[70] described 29 adult patients with Streptococcus agalactiae (group B streptococcus) bacteremia reviewed over 10 years at the Walter Reed Medical Center. Nine (31%) of these bacteremic patients had diabetes, and six of these had involvement of the urinary tract.

Renal papillary necrosis is a well-known complication of UTIs in diabetic patients. More than half of patients with renal papillary necrosis are diabetic, possibly reflecting microvascular insufficiency leading to ischemia and necrosis of the renal papilla.[71] These patients may present with flank pain, chills, and fever, and 15% may have renal insufficiency.[59]

25.2 Manifestations of Urinary Infections in Patients with Diabetes Mellitus

Clinical Manifestation	References
Asymptomatic bacteriuria	59,60,61,172
Acute papillary necrosis	59,71
Bacteremia	62, 65
Emphysematous cystitis	72,173,174
Emphysematous pyelonephritis	73–76,174,175
Fungal infections	176,177
Perinephric abscess	178,179
Xanthogranulomatous pyelonephritis	128,180

Emphysematous infectious processes may involve the bladder (emphysematous cystitis) or the kidney (emphysematous pyelonephritis) and are more frequent in diabetic patients. Emphysematous cystitis is usually caused by common facultative bacteria such as E. coli, although a few cases caused by Clostridium perfringens have been reported.[72] This condition is identified on plain films, urographic roentgenograms, or CT scans by finding gas in the bladder wall. Tissue ischemia or trauma is usually involved in the pathogenesis.

Emphysematous pyelonephritis usually results from an invasion of the renal parenchyma by gas-producing organisms. In patients with diabetes mellitus, high levels of blood glucose offer an enhanced environment for bacteria, and gas formation may result from the accompanying mixed acid fermentation of glucose by enteric organisms. In patients with diabetes, emphysematous pyelonephritis presents with fever, chills, flank pain and tenderness, and often the finding of a flank mass or a gas-containing renal mass on imaging studies.[73,74] E. coli is the most frequently isolated bacteria, followed by Proteus, Pseudomonas, and Klebsiella spp., with Clostridium spp. and Candida spp. reported occasionally. The diagnosis is established by the radiologic finding of gas in the renal parenchyma and bacteremia is usually present. Urine cultures are positive, and renal failure and hematuria may occur.[75,76]

Treatment includes intravenous fluid support, appropriate intravenous antibiotics, and percutaneous or renoureteral catheter drainage.[74–77] Hyperbaric oxygen might be useful as an adjunct to antibiotics.[78] Laparoscopic or open nephrectomy may be required if the response to medical therapy is delayed, especially in patients with extensive renal involvement and/or multiorgan system dysfunction. Emergency nephrectomy in these patients carries a high mortality and should be delayed for antibiotic treatment if possible.[74–77]

Renal Transplantation

UTIs may occur in patients following renal transplantation, with an incidence rate as high as 80% in some series.[79,80] Most of these infections occur within the first 6 months following transplantation and are usually caused by common Enterobacteriaceae, including E. coli, Klebsiella pneumoniae, or by P. aeruginosa, or fungi, especially Candida spp. and Aspergillus spp. Infections that occur 6 months or later after transplantation are less common and are more likely to involve the lower urinary tract, including the bladder. UTIs due to anaerobes, Ureaplasma urealyticum, and Gardnerella vaginalis have been reported posttransplant and the latter was implicated as a cause of a perinephric abscess in one patient.[81] Transmission of multidrug resistant (MDR) E. coli during kidney transplantation has been reported recently. A donor with MDR E. coli caused infection in two different kidney recipients. One developed sepsis and a complicated UTI, the other developed a perinephric abscess. This resulted in renal graft failure in both patients, but both survived.[82]

Risk factors for posttransplant UTIs include advanced age, pretransplant UTIs, female gender, diabetes mellitus, postoperative instrumentation and catheterization, cadaveric donors, intraoperative ureteral stents, immunosuppression, and acute graft rejection.[80,83]

In the early posttransplantation period, symptoms of a urinary infection may be mild or absent and fever may be absent; however, pyelonephritis and associated bacteremia are not uncommon.[79] Uremia and corticosteroid or other immunosuppressive therapy may contribute to this situation. Posttransplantation renal infection (especially with Enterococcus faecalis and occurring 6 months or more after a transplant) may lead to elevated serum creatinine levels and may result in a cascade of immunologic responses that ultimately precipitate allograft dysfunction or rejection.[80,83] In addition to common cytomegalovirus infections in transplant patients, infections with hepatitis C virus and BK polyomavirus have been described after renal transplantation, and viral-associated interstitial nephritis may occur. In one center, BK polyomavirus with an associated transplant dysfunction and a graft loss was reported in 2.5% of transplanted patients. Clinical features include ureteral obstruction, lymphocele, bacterial urinary infection, and hematuria. The diagnosis may be established with renal biopsy and electron microscopy of urine. Interruption of the progression may be achieved with immunosuppressive treatment.[84,85] Relapse rates may be high if posttransplantation urinary infections are not treated aggressively with antimicrobial agents.

Chronic urinary infections may occur in these patients and can be particularly problematic if associated with anatomic or structural defects in the ureter, bladder, or urethra as a result of the surgical procedure itself or secondary to a fistula formation. Vesicoureteral reflux may develop at the ureteral anastomotic site in up to 25% of patients and may lead to hydronephrosis and infection. Graft failure may also occur as a result of mesangiocapillary glomerulopathy.[86,87]

Prophylactic use of trimethoprim-sulfamethoxazole for 6 months following a renal transplantation may prevent complicated UTIs, including gram-negative rod bacteremia and sepsis[79,80,88,89] and may decrease the incidence of posttransplantation urinary infection to less than 10%. This drug also might reduce the development of opportunistic infections caused by Listeria monocytogenes, Nocardia asteroides, and Pneumocystis jiroveci.[79,80] However, reports of trimethoprim-sulfamethoxazole–induced alteration of renal function or synergistic exacerbation of cyclosporine nephrotoxicity have stimulated the search for other prophylactic compounds.

The treatment of pyelonephritis in the posttransplantation patient should include 6 weeks of an appropriate antibiotic based on susceptibility testing plus chronic "suppressive" antibiotic therapy thereafter.[79] A late UTI after renal transplantation may be a risk factor for serious complications including graft loss and death as described in a retrospective review of 728,000 renal transplant patients.[91]

Pharmacokinetic or pharmacodynamic interactions between ciprofloxacin and cyclosporine have not been reported, which suggests that they can be used together without additional monitoring.[90]

Patients are at increased risk of catheter-associated urinary infection because they often receive Foley catheters in the post-transplantation period. Catheter-tip cultures have been used to screen for these infections. Tolkoff-Rubin and colleagues[89,92] used prophylactic trimethoprim-sulfamethoxazole (160 mg of trimethoprim, 800 mg of sulfamethoxazole) for 4 months after urinary catheter removal and reported a decrease in the catheter-associated infection rate from 38% to 8%.

Spinal Cord Injury and Neurologic Dysfunction

Frequent bladder catheterization is necessary as a result of bladder neuropathy in paraplegic or quadriplegic patients following traumatic or surgical injury to the spinal cord. This leads to colonization of the lower urinary tract with pathogenic bacteria and results in bacteriuria in about 80% or more of these patients.[93] Bacteremia may follow and urinary infection may be associated with high mortality rates in patients with spinal cord injury and neuropathic bladders.

Urinary infections and the related sepsis as well as the high frequency of renal disease in these patients are probably associated with vesicoureteral reflux, hydronephrosis, accompanying renal calculi, and pyelonephritis, which are often responsible for death.

These patients may not present with typical symptoms of fever, chills, dysuria, or flank pain, and the presence or absence of symptoms usually is not helpful in predicting the results of urine cultures. Perkash and Giroux[94] found typical symptoms in only 3% of 110 patients with spinal cord injury and bacteriuria ($>10^5$ bacterial colonies per milliliter).

The prevention of infection in patients with spinal cord injury is a major priority. Unfortunately, intermittent catheterization or self-catheterization as an alternative to indwelling bladder catheters may be associated with complications, including urethral fistulization, stricture, periurethral abscess formation, and epididymitis.[3] Although several older publications reported modest success with methenamine compunds[95] or with some antibiotics including trimethoprim-sulfamethoxazole,[96] the current IDSA guidelines do not support these modalities in long-term catheterized patients.[3] In almost every case, modest reduction in bacteriuria or symptomatic infection was associated with an increased risk of antimicrobial resistance. Bladder irrigants are also not recommended and neither is routine screening for bacteriuria in these patients.[3]

The IDSA guidelines do recommend that a urine culture be obtained prior to treatment in catheterized patients who do develop symptomatic UTIs. Replacement of the catheter prior to the onset of treatment can hasten the response and can minimize the occurrence of polymicrobic bacteriuria. Optimal culture results are obtained through the replacement catheter. These guidelines recommend treatment for several days if the clinical response is prompt, or 10 to 14 days if not. The specific antibiotic choice should be made according to susceptibility test results.[1]

Recent attention to the development of adherent biofilms in the urinary tract may offer explanations for recurring and difficult-to-treat infections in this population. Uropathogens can develop dense urethral biofilms with glycocalyx material on the bladder wall or catheters. Recently, biofilms have been described with intracellular bacteria that cause bulges appearing like pods on the bladder surface of infected mice. The pods have been shown to have polysaccharide matrices with a protective shell of uroplakin. It is becoming increasingly more evident how bacteria may evade antimicrobial killing within an environment that protects microorganisms in a uroplakin shell. These mechanisms support the ability of biofilms to allow bacterial microcolonies to survive and cause chronic or recurrent infections.[97,98] This may contribute to the pathogenesis of recurrent urinary infections. Bacterial biofilms also can be detected on bladder epithelial cells and may respond better to fluoroquinolones than to trimethoprim-sulfamethoxazole. In addition to the clinical cure of urinary infections, ofloxacin eradicated bladder biofilms in patients with spinal cord injury.[99] Although silver alloy-hydrogel coated catheters might reduce biofilm formation and delay bacteriuria, they have not yet been shown to reduce bacteriuria or UTIs in patients with neurogenic bladders who require long-term catheterization.[100] Increasing antibiotic resistant gram-negative bacteria and MDR staphylococci are being reported in outpatients with spinal cord injury and UTIs.[101]

An experimental approach to prophylaxis has been reported that uses a nonpathogenic E. coli strain 83972 to colonize urinary bladders in spinal cord injury patients. Intravesical inoculation and colonization with this bacteria was not associated with urinary infection symptoms but was associated with an improved quality of life.[102] Other approaches, including cranberry products, may lead to a reduction of uroepithelial cell biofilms,[103] but these are not recommended in the IDSA guidelines because supporting data were not definitive.

As mentioned already, frequent monitoring and the treatment of symptomatic infection with appropriate bactericidal antibiotics may reduce the morbidity of urinary infections in spinal cord–injured patients with long-term indwelling catheters.

Neutropenia

Patients whose neutrophil count has fallen below 1,000 granulocytes per microliter are at an increased risk of bacterial infections. Most of these patients have received anticancer chemotherapy for leukemia, lymphoma, or solid tumors. The gastrointestinal (GI) flora is the usual source of bacteremia in these patients, and unless instrumentation in the urinary tract has been performed, urinary infections are not particularly frequent. In a recent series, about 6% of the infections in neutropenic patients arose from the urinary tract.[104] In patients with profound and prolonged granulocytopenia

(<100 cells per microliter), bacteremia is not uncommon; however, the urinary tract is infrequently the source of these infections. In fact, bacteremia in this population is more frequently caused by gram-positive cocci than gram-negative rods, probably in part because of the presence of chemotherapy-induced oral mucositis and the dissemination of oral gram-positive cocci to the bloodstream.

The usual symptoms and signs of bacterial urinary infection may not be manifest because granulocytopenic patients may not respond locally to the presence of infection. Dysuria and burning may or may not be present, and pyuria is often minimal because of the absence of granulocytes[105]; therefore, it is important to culture the urine in febrile granulocytopenic patients even though the yield may be low. Fungal urinary infections may occur, especially following long courses of antibiotics. Patients with hematologic malignancies and neutropenia have been reported to have Achromobacter and Alcaligenes spp. bacteremic infections, with urinary tract involvement or origin. Resistance patterns for these species show susceptibility to antipseudomonal penicillins, carbapenems, and trimethoprim-sulfamethoxazole, but resistance to fluoroquinolones and aminoglycosides.[106]

The empirical use of antimicrobial agents early in the course of a fever after appropriate cultures of blood, urine, and material from other presumed infected sites are obtained has reduced the mortality owing to infections in neutropenic patients. A Gram stain should be performed on urine specimens from these patients and antibiotics directed against the common bacterial pathogens in this population, such as E. coli, S. aureus, P. aeruginosa, and streptococci (especially viridans Streptococcus). Fluconazole or amphotericin B should be considered for candidal UTIs, but the new echinocandins do not achieve adequate concentrations in the urine.

AIDS and HIV Infection

AIDS and infection with HIV have been associated with infectious and noninfectious complications in the GU tract.[107–109] Noninfectious complications include HIV-associated nephropathy, which has become the third leading cause of end-stage renal disease in African Americans between 20 and 64 years old, but the progression of HIV nephropathy has been slowed by the use of highly active antiretroviral therapy (HAART).[110] Acute renal failure also develops in HIV-infected patients at rates that are enhanced at lower CD4 counts and are decreased with antiretroviral therapy.[110–112]

Other noninfectious complications are associated with antiretroviral drugs, especially protease inhibitors, and are usually used in combination with two other highly active agents to prevent HIV replication. Indinavir sulfate has been implicated with crystallization and stone formation in the urinary tract, which is not usually visible on plain radiographs. Patients complain of ipsilateral flank pain with nausea, vomiting, dysuria, and hematuria. CT scans are not diagnostic, but calcifications may be seen ultrasonically in approximately 35% of cases. Up to 20% of patients treated with indinavir may have urologic side effects. Conservative treatment with hydration, analgesia, and a brief discontinuation of therapy is effective, but permanent withdrawal may be necessary in 5% of patients.[113] Tenofovir and lopinovir-ritonavir combinations have been associated with an increased risk of acute renal failure (ARF), and renal function should be monitored during therapy.[114] However, more recent studies have suggested that these drugs were not as predictive of ARF as were levels of immunodeficiency.[110–112, 115]

Infections caused by commonly encountered bacteria are frequent and may present as cystitis, pyelonephritis, or renal abscesses. Also, Mycobacterium tuberculosis as well as atypical or nontuberculous mycobacteria may be found in upper and lower UTIs in these patients. Of the usual infecting bacteria, E. coli accounts for the most, and Pseudomonas, Proteus, Klebsiella, Enterobacter spp., and Enterococcus spp. are found frequently. Acinetobacter, Salmonella, and Candida spp., Aspergillus spp., Cryptococcus spp., and Mycobacterium spp. also may be encountered and should be looked for in patients whose CD4 counts are <500 or who do not respond quickly to antibiotics.[107,108] Upper and lower UTIs are probably more common in HIV-infected than in non-HIV-infected patients.[107,108]

Urethritis, prostatitis, and prostatic abscesses may occur due to infections with S. aureus, Enterococcus spp., Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, and Histoplasma capsulatum.[107,116] In the case of a histoplasma abscess, urine cultures are positive only rarely. Granulomatous interstitial nephritis resulting from disseminated histoplasmosis has been reported.[117] Microsporidial infection of the urinary tract caused by Vittaforma corneae has been described.[118]

Urinary infection with Aspergillus presenting as a renal aspergilloma has been reported in an AIDS patient who was treated successfully with amphotericin B instillation via a nephrostomy tube, as well as with systemic antifungals.[119] Nosocomial infections with Stenotrophomonas maltophilia of presumed urinary tract origin have been reported in HIV-infected patients and were associated with high-level resistance to β-lactam antibiotics, monobactams, carbapenems, and aminoglycosides.[120]

Cytomegalovirus can cause cystitis with hematuria in HIV-infected persons,[92] and toxoplasmic cystitis also has been described.[121] Trichomonas vaginalis urethritis, documented both by wet-mount and culture and polymerase chain reaction, has been reported in men with and without symptoms.[122] Latent urinary BK virus, a human polyomavirus, can be activated in patients with AIDS, and nephritis may result.[123] Adenovirus hemorrhagic cystitis with gross hematuria and dysuria has been described in an HIV-infected patient with Burkitt lymphoma.[124] Noninfectious vesicle involvement with Kaposi sarcoma and urethral lymphoma in HIV-infected patients may have unusual presentations that initially could be confused with urinary infection.[108]

Patients with a neurogenic bladder that complicates HIV infection or AIDS may present with urinary retention, urinary frequency, and altered urinary flow as a result of bladder hyperreflexia or hyporeflexia. Most of the patients

with bladder hyperreflexia had concomitant cerebral toxoplasmosis.[125] Other patients with AIDS may have urinary retention secondary to central nervous system lymphoma, myelopathy, or prostatic hypertrophy. The incidence of many of these conditions has declined with the use of HAART.

MISCELLANEOUS CAUSES

Pyonephrosis is an acute suppurative infectious process with gross pus within the renal parenchyma that usually results from ureteral obstruction.[126] The clinical differentiation of pyonephrosis from infected hydronephrosis is difficult even with the use of ultrasound evaluation, but the finding of fluid-debris levels on MR urography is a strong indicator of pyonephrosis.[127] This infection may be associated with an obstruction secondary to congenital anomalies, calculi, malignancy, ureteral strictures, nephrolithiasis, diabetes, and functional disorders of the renal collecting system.

In a review of 23 patients with pyonephrosis, 15 patients presented with virgin stone formation that produced an obstruction at various sites including the calyces, renal pelvis, and middle and distal aspects of the ureter.[126] Clinical presentation may vary from asymptomatic bacteriuria to resembling that of pyelonephritis with fever, flank or abdominal pain, leukocytosis, pyuria, and septic shock. The responsible organisms include Enterobacteriaceae and anaerobic bacteria such as Bacteroides spp., and Candida spp.

Radiographic determination of pyonephrosis may be limited even with the use of ultrasonography and CT; the correct diagnosis requires a high degree of suspicion, and MR urography may be helpful.[127] Ultrasound or CT-guided renal urine aspiration or retrograde ureteral catheter placement may be required. Nephrectomy may be necessary if drainage and appropriate antibiotic therapy directed at organisms isolated from aspirated and drained infected material does not prove successful.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a unique pathologic presentation of chronic bacterial pyelonephritis. Schlagenhaufer initially described it in 1916, and more than 500 cases have been reported in the literature. However, xanthogranulomatous pyelonephritis remains relatively uncommon and accounts for less than 1% of surgically or pathologically proved cases of chronic pyelonephritis. Most cases are diagnosed in elderly patients, with almost 70% occurring in women. A recent review highlighted the risk factors for xanthogranulomatous pyelonephritis, which included female gender, obesity, elevated creatinine, and the presence of renal stones or staghorn calculi.[128]

The pathogenesis of xanthogranulomatous pyelonephritis is uncertain. Although P. mirabilis infection is present in most patients, it is not essential for the pathologic process to occur. Urinary obstruction usually has a role. Macrophages filled with periodic acid-Schiff (PAS)-positive granules have been produced in a rat infection model with P. mirabilis, E. coli, and S. aureus. On electron microscopy, macrophages appear to have ingested bacteria and developed phagolysosomes filled with amorphous material. It is hypothesized that xanthogranulomatous pyelonephritis may be caused by a lysosomal defect of macrophages that prevents the complete digestion of ingested bacteria. Familial disease has not been described.

Presenting symptoms are recurrent flank pain, fever, and constitutional fatigue. Persistent anemia and leukocytosis occur in about 75% of patients. The urinalysis shows pyuria and, often, hematuria. Urine cultures are positive for P. mirabilis in about two-thirds of patients, and E. coli, Klebsiella spp., and S. aureus are each reported from a small proportion of patients. Multiple pathogens occur in about 25% of patients. In a small proportion of patients, urine cultures are negative despite ongoing disease activity, and positive cultures may be obtained from resected renal tissue.[129] S. aureus may produce localized disease that might not be associated with nephrolithiasis, and MRSA infections have been reported.[130] Occasionally, pathogens isolated from resected renal tissue are different than those from voided urine.[129]

Most patients have a history of recurrent urinary infection, often complicated by renal calculi, obstructive uropathy, and previous urologic procedures. Often, patients have had a chronic undiagnosed illness for several months before the diagnosis of xanthogranulomatous pyelonephritis has been considered. On physical examination, a renal mass is palpable in more than 50% and hypertension is present in about 25% of patients.

Intravenous pyelography (IVP) discloses a nonfunctioning kidney in 85% of patients. Struvite renal calculi occur in 80% and are virtually universal with P. mirabilis infection. Radiologic investigation may also demonstrate cavitary masses and calyceal deformities. Angiography usually discloses hypovascular renal masses with no neovascularization. CT scan is the diagnostic procedure of choice. It demonstrates the extent of involvement of perirenal structures and may permit a specific diagnosis by the recognition of abnormal fatty tissue in the renal mass.

The disease is almost always unilateral and appears to be caused by chronic renal infection with an unusual inflammatory response. On a gross examination, the kidney is enlarged with either local or generalized involvement of renal tissue. Calyces are usually dilated and the renal parenchyma is replaced by yellow-orange soft tissue, which is usually surrounded by abscesses. The localization of this peculiar tissue in the renal pelvis is characteristic. Perirenal fat is usually inflamed, edematous, and adherent to the kidney. The inflammation may spread beyond Gerota's fascia and involve the perirenal fat of the retroperitoneal space. On a microscopic examination, the lipidlike tissue is composed of a mixture of large foamy lipid-laden macrophages (xanthoma cells) together with neutrophils, plasma cells, fibroblasts, and necrotic debris. The cytoplasm of the xanthoma cells stains strongly with PAS. Although these cells form the basis of the microscopic identification of the lesion, they are not specific

and may only reflect phagocytosis of tissue within the lipid. Foreign-body giant cells and microscopic calcification are also frequently present.[129]

Xanthogranulomatous pyelonephritis is frequently mistaken for renal carcinoma or renal tuberculosis. Prior to the availability of CT scanning, the diagnosis was seldom considered preoperatively. Kidneys were often removed surgically because of an incorrect preoperative diagnosis. Current organ imaging technologies enable a preoperative diagnosis. If the disease is localized in the kidney, total nephrectomy may be avoided, and local resection with the removal of renal calculi and intensive treatment of the urinary infection may salvage residual functioning renal tissue.[129] The disease rarely involves both kidneys and does not recur after treatment. The disease has not been observed to progress serially from one kidney to the other, so the radical removal of involved tissue is not necessary. Laparoscopic approaches have been successful,[131] and a recent case report documents successful treatment with antibiotics alone in a patient with leukemia and a splenic abscess.[132]

Malakoplakia

Renal malakoplakia is a rare granulomatous disease of uncertain etiology that occurs in similar clinical settings to xanthogranulomatous pyelonephritis. The term malakoplakia is derived from the Greek word for soft plaque. Over 200 cases have been reported to date, predominantly in women and the elderly. Many of the clinical and laboratory features of this disease resemble those of xanthogranulomatous pyelonephritis, but most patients have an E. coli rather than a P. mirabilis urinary infection.[133]

The gross lesion is a soft yellow-brown plaque of variable size. Renal tissue is involved in one-fifth of patients and is bilateral in about 50%. The renal pelvis and ureters are involved in an additional one-fifth of patients, and a ureteral stricture may develop. Renal involvement appears frequently to be an ascending progression of bladder malakoplakia. Histologically, the plaques show large histiocytes with a foamy eosinophilic cytoplasm, called von Hansemann macrophages. The cytoplasm contains PAS-positive granules and large renal concentric crystals, named Michaelis-Gutmann bodies, which differentiate malakoplakia from xanthogranulomatous pyelonephritis.[134] These bodies show a typical crystalline structure on electron microscopy and are primarily calcium and iron on chemical analysis. These lesions may be confined to the urinary tract but occasionally are seen on the skin, in the prostate, testes, and the gastrointestinal tract.

The disease is caused by a defect in macrophage function, with impairment of bactericidal activity of monocytes for E. coli, and this organism may play a particular role in its pathogenesis.[134,135] The movement of lysosomes to phagocytic vacuoles is delayed owing to low levels of cyclic guanosine monophosphate. A cholinergic agonist, such as bethanechol, can correct this defect.[136,137] The Michaelis-Gutmann bodies are presumed to result from the abnormal deposition of calcium phosphate and iron in the overloaded phagosomes.[134]

Renal parenchymal malakoplakia usually occurs as an upper tract infection with fever and flank pain or tenderness.[134–136] A palpable flank mass may be present. Imaging reveals enlarged kidneys with multiple filling defects. Renal malakoplakia may progress to renal impairment and failure. The disease occurs more frequently in immunosuppressed patients and has been observed in several patients following renal transplantation.[134,137]

Several patients have been treated successfully with the cholinergic agonist bethanechol chloride and long courses of trimethoprim-sulfamethoxazole or a fluoroquinolone.[134–137] Immunosuppression may have to be modified when the disease occurs in renal transplant recipients.

Urosepsis

The urinary tract is the most common site of origin for gram-negative rod bacteremia, and the development of bacteremia from a urinary focus is termed urosepsis. Urosepsis is one of the most common presentations for bacteremic illness in nursing homes and hospitals. As discussed already, E. coli accounts for almost half of these uroseptic infections, with other enteric gram-negative bacilli and enterococci following in frequency. Interleukin 8 (IL-8), a small chemotactic protein, plays an important role in neutrophil migration during a UTI and increased urinary interleukins occur in urinary tract infections and urosepsis.[138,139] A recent report even suggests that urinary IL-8 can be used for the rapid diagnosis of urosepsis in children.[140] Patients with acute pyelonephritis have higher IL-8 levels in the urine than in the plasma. During urosepsis, this phenomenon stimulates the delivery of neutrophils to the GU system and results in pyuria. Serum IL-1 receptor antagonist, IL-10, and soluble tumor necrosis factors are elevated in urosepsis, suggesting a systemic anti-inflammatory response.[141] Although endotoxin (the bacterial cell wall lipopolysaccharide) may enter the circulation from a well localized focus of gram-negative bacterial infection, the presence of sepsis originating from the urinary tract usually implies bacteremia, which in turn usually results from an infection in the kidney or the renal pelvis.

Clinically, most uroseptic patients present with fever, shaking chills, flank pain, hypotension, cloudy urine, and leukocytosis. However, obtunded patients may not have urinary complaints or clinical signs referable to the urinary tract, and patients with obstructive uropathy might not present with the usual laboratory clues of pyuria and bacteriuria. Bacteremia in a patient with a urinary infection usually implies that the infection originates from the kidney, but in the presence of an indwelling bladder catheter, erosive urethritis or cystitis might be the responsible focus. Also, sepsis may follow the instrumentation or manipulation of the lower urinary tract such as occurs during a percutaneous nephrolithotomy or a ureteroscopy. Staghorn calculi (struvite or apatite) can become embedded with gram-negative bacteria. A recent study identified endotoxins associated with sepsis in stone fragments in a child who died from sepsis syndrome after percutaneous staghorn stone manipulation.[142]

The diagnosis of urosepsis is usually confirmed by blood cultures positive for the same organism cultured from the urine. Despite initial hopes that rapid diagnostic tests for the presence of a circulating endotoxin might speed the diagnosis of bacterial sepsis, no such test is available currently. A careful examination for the presence of bacteria on a drop of unspun urine (under a cover glass, or a gram-stained smear) plus the findings of pyuria in a septic patient point to the urinary tract as the source of the infection in most cases. However, strong clinical suspicion is necessary for less typical patients and at least two and preferably three blood cultures should be obtained to identify the responsible organism.

Treatment requires intravenous fluid support, the maintenance of blood pressure with pressors if necessary, and antibiotics. If the organism is known (as in the case of recently cultured urine in a septic patient), then a single active antibiotic can suffice. If no clues exist as to the identity of the organism, intravenous therapy with an extended-spectrum penicillin (e.g., piperacillin), a penicillin-penicillinase inhibitor combination (e.g., ticarcillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam), or a carbapenem (e.g., imipenem, ertapenem, meropenem, doripenem) can be used. Third-generation cephalosporins also can be used, but these agents are not effective against enterococci. Aminoglycosides (gentamicin, tobramycin, or amikacin) may be used in combination with a β-lactam if enterococci or P. aeruginosa are suspected. Combination therapy with a third-generation antipseudomonal cephalosporin such as ceftazidime, or a carbapenem or an extended-spectrum penicillin plus aminoglycoside is suggested if gram-negative rod bacteremia occurs in a patient with granulocytopenia. Intravenous fluoroquinolones (e.g., ciprofloxacin, levofloxacin) also are useful, but resistance is increasing in many centers. Carbapenems have extended activity against gram-negative bacilli, although ertapenem has limited activity against Pseudomonas aeruginosa.[143]

β-Lactamase–mediated carbapenem resistance has been well described in Klebsiella pneumoniae and other Enterobacteriaceae, and these organisms as well as Acinetobacter spp. are widely spread in hospitals.[144,145] Multiple antibiotic resistance is common in these organisms, including resistance to aminoglycosides, cephalosporins, and fluoroquinolones. Some might retain susceptibility to carbapenems, but polymyxin or colistin might be needed to eradicate MDR bacteria.[146] Nephrotoxicity and neurotoxicity warrant caution with these antibiotics.

A new glycylglycine, tigecycline, has antibacterial activity against some MDR bacteria, as well as ESBL-producing Acinetobacter, MRSA, and vancomycin-resistant enterococci. However, tigecycline is unstable in urine and is not used as a first-line agent if gram-negative rod bacteremia originates in the urinary tract.[147,148]

Adjunctive therapy with corticosteroids is not recommended. Considerable research activity has been directed to blocking cytokine activity in sepsis (not limited to urosepsis), but recent trials of antiendotoxin monoclonal antibodies, antitumor necrosis factor antibodies, and IL-1 receptor antagonists have been disappointing.

Others

Tuberculosis (Chapter 27) and renal and perinephric abscesses (Chapter 24) also are discussed elsewhere. Abscesses may rarely develop in the bladder wall. These intramural vesicle abscesses are only rarely reported and are usually caused by coliform bacteria, often in the presence of inflammatory bowel disease, diverticular disease, or a foreign body.

Infections Caused by Unusual or Resistant Organisms

In the face of increasing bacterial resistance to many antibiotics, the treatment of complicated UTIs is less simple given the resistance to fluoroquinolones, TMP-SMX, and β-lactams.[1,149] At least 4 weeks of therapy may be needed and the treatment choice must be based on susceptibility testing. Enterococci are not uncommon causes of UTIs, and GU sites account for the majority of clinical bacteriology laboratory isolates. These organisms are more commonly isolated from nosocomial infections than from the community. Enterococci may be the causative agents in lower UTIs (e.g., cystitis), in catheter-related infections, in infections following urinary tract instrumentation, and in patients with GU anatomic abnormalities.[150,151]

The incidence of enterococcal infection, in general, is increasing at an alarming rate according to the National Nosocomial Infection Surveillance (NNIS) Study; for example, from 1980 to 1989, the incidence of bloodstream infections with enterococci has increased 120%,[149,151,152] and the urinary tract is frequently identified as the source. These infections may originate from the patient's own GU or GI flora or may be nosocomially spread from other patients.

Unfortunately, antimicrobial resistance in enterococci is also increasing dramatically, not unlike the rise in methicillin-resistant S. aureus seen over the past 30 years. A large number of enterococcal strains, especially Enterococcus faecium, show vancomycin resistance. This has been attributed to the almost 160-fold increase in vancomycin usage per 1,000 patient-days in hospitals between 1978 and 1992.[153] Vancomycin resistance is often classified by phenotypic expression of the presence of certain resistance genes such as VanA, which mediates resistance to vancomycin and teicoplanin; VanB with strains susceptible to teicoplanin but resistant to vancomycin; and VanC, which imparts low-level resistance to vancomycin in strains of Enterococcus gallinarum and Enterococcus casseliflavus.[154]

Also, enterococcal strains that were previously susceptible to penicillin and gentamicin have been identified. Even penicillin plus gentamicin therapy may fail to eradicate some of these infecting organisms.[154] Although vancomycin had been used as a mainstay in the therapy of complicated nosocomial enterococcal urinary infections, vancomycin-resistant

E. faecium and E. faecalis threaten the use of this drug. Alternative treatments with drugs such as linezolid or quinupristin-dalfopristin are effective against vancomycin- and penicillin-resistant E. faecium; nitrofurantoin or fosfomycin trometamol may be effective in simple UTIs.[155,156] Vancomycin-resistant E. faecalis may be treated with a penicillin, nitrofurantoin, or fosfomycin. MDR enterococcal infections may be treatable with linezolid, daptomycin, or tigecycline, but the emergence of resistance is possible.[155–158] Daptomycin is also active against MRSA.[159] Recent publications do not recommend the routine treatment of asymptomatic enterococcal bacteriuria.[155] Increasing MDR strains of E. coli causing community-acquired pyelonephritis and other complicated UTIs are being reported, with identified clonal groups and widespread circulation of ESBL-producers responsible for the antimicrobial resistance.[160–161] Some of these organisms might be treatable with carbapenems (imipenem, meropenem, doripenem, ertapenem) or they might require colistin treatment.[146,162]

Hemolytic-uremic syndrome (HUS) associated with enterohemorrhagic E. coli urinary infections has been reported. Hemolytic-uremic syndrome includes a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal impairment. Thirteen cases of HUS associated with E. coli UTIs have been described. Most of these cases were not associated with diarrhea or a prodrome, which usually occur when HUS occurs as a result of the consumption of fecally contaminated products from cattle or sheep.[163] A few other cases have been reported,[164] but routine screening for shiga toxin–producing E. coli is not recommended.[165]

Atraumatic ruptures of the urinary bladder associated with MRSA have been reported.[166] MRSA UTIs usually require therapy with intravenous vancomycin. Involvement of the upper urinary tract, pyelonephritis, renal abscess, and bacterial endocarditis should be excluded in these patients. Bladder ruptures have been reported as a result of a Candida tropicalis bezoar[167] and secondary to a multiorganism infected urachal cyst.[168]

Anaerobic bacteria are unusual causes of urinary infection, but they are implicated in some patients with genitourinary abscesses, scrotal gangrene, and in patients with urinary diversions.[169,170] Although they are major components of the normal urethral, periurethral, and vaginal flora, their presence in these areas may prevent other, more invasive aerobic or facultative organisms from colonizing these sites and subsequently causing infection. Anaerobic bacteria may be identified in the urine in chronically catheterized patients but this is often short lived and without clinical significance; however, anaerobic bacteriuria is more frequent in patients who have undergone a renal transplantation.[171] Anaerobes that have been implicated in complicated UTIs include Bacteroides fragilis, B. melaninogenicus, Fusobacterium nucleatum, Peptococcus spp., Peptostreptococcus spp., and Clostridium perfringens, among others.[169]

The mechanism by which these organisms cause disease in the bladder, kidney, or prostate depends on their ability to ascend from the periurethral area to the bladder or kidney. This process is accelerated in the presence of obstruction, urinary stasis, calculi, trauma, and catheters or other foreign bodies. Anaerobic bacteria have been documented to cause prostatitis and prostatic abscesses as well as bacteriuria, pyelonephritis, and urosepsis. Some of these organisms (e.g., Bacteroides or Sphaerophorus spp.) have been implicated in urinary or prostate infections following colonic surgery.[169] Clindamycin and metronidazole are usually active against most anaerobic organisms (although resistance is increasing) and cefoxitin or cefotetan, carbapenems, and β-lactams with β-lactamase inhibitor combinations also may be effective. The surgical correction of underlying causes is often required.

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