Urinary Tract Infection (UTI)

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Urinary tract infections (UTI) are a major cause of morbidity, mortality, and increased health care costs [1 – 3]. They can cause a wide variety of clinical manifestations ranging from asymptomatic bacteriuria to simple cystitis to life-threatening illnesses including sepsis [4]. Recent approaches to UTI treatment have emphasized protocols for management without office visits and short-term antibiotic therapy in women with uncomplicated cystitis, as well as awareness of the impact of emergence of resistant bacteria. To achieve optimal efficacy while limiting costs and the potential for adverse drug effects, the health care provider must tailor therapy with consideration of host status, probable infecting organisms, resistance patterns in the local community, and currently recommended practice guidelines [2, 5, 6].

Asymptomatic Bacteriuria

Bacteriuria unaccompanied by UTI symptoms is present in 1 – 3% of young women but < 0.1% of young men. Increasing percentages of both men and women develop bacteriuria as they age. At least 10% of elderly men and 20% of elderly women have asymptomatic bacteriuria [7]. Bacteriuria is nearly universal in chronically catheterized patients. Under most circumstances, if the patient does not have symptoms of UTI such as dysuria or fever, bacteriuria should not be treated with antibiotics, regardless of the presence or absence of pyuria [2].

Nevertheless, asymptomatic bacteriuria does require treatment in some groups of patients. Specifically, it is important to treat children with asymptomatic bacteriuria to decrease the chances of renal damage and long-term renal insufficiency. Patients scheduled to undergo urinary tract instrumentation or surgery should also be screened, and if found to have asymptomatic bacteriuria, they should be treated with antibiotics to reduce the risk of procedure-induced urosepsis [2]. Up to 20% of pregnant women with asymptomatic bacteriuria may develop pyelonephritis. For this reason, routine screening of urine and treatment of asymptomatic bacteriuria are components of appropriate prenatal care [6, 8, 9]. Asymptomatic bacteriuria in these patient groups should be treated based on the results of susceptibility testing, usually with a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX), oral fluoroquinolones (avoid in pregnancy and children), amoxicillin, nitrofurantoin, or an oral cephalosporin. Some authors also recommend that other patients at particular risk for severe consequences of infection, such as neutropenic patients, should be treated with antibiotics if they develop asymptomatic bacteriuria.

Early observations associating asymptomatic bacteriuria with increased mortality in the elderly raised concerns that this condition

might contribute to mortality. However, it is now well substantiated that a causal connection cannot be established between asymptomatic bacteriuria and mortality in the elderly [7, 10]. Furthermore, treatment of such patients with antibiotics is quite ineffective in producing lasting urinary tract sterility. In fact, treatment of asymptomatic bacteriuria in the elderly has been shown to be associated with adverse medication effects, selection of resistant organisms, and possibly increased mortality [6].

Nonantibiotic approaches to the prevention of bacteriuria have been attempted, including use of estrogen replacement therapy for elderly women and cranberry juice consumption in the elderly. Oral or topical estrogen replacement therapy in postmenopausal women with recurrent UTI reduces the frequency of bacteriuria, possibly because of the effectiveness of such therapy in restoring a premenopausal vaginal microenvironment and diminishing vaginal colonization with coliform bacilli [11]. Daily consumption of cranberry juice for 6 months significantly decreased the prevalence of bacteriuria among elderly residents of a home for senior citizens [12]. However, most of the episodes of bacteriuria were asymptomatic, so the clinical value of the observed preventive effect could be questioned. Nonetheless, there were trends towards decreased antibiotic use and fewer symptomatic UTI episodes in the treatment group, suggesting that the intervention may have provided a meaningful benefit.

Symptomatic UTI

Symptomatic UTIs range from simple cystitis to pyelonephritis to invasive febrile UTI with bacteremia [3, 13]. UTIs may be further classified as uncomplicated or complicated by the presence of anatomic or functional abnormalities of the urinary tract or by underlying medical illnesses. In practice, it is often difficult to definitively classify patients into one of these categories. The important principles are that it is critical to treat all symptomatic UTIs and that the required intensity and duration of therapy increase in proportion to the severity of the clinical syndrome (Table 1) [3, 6]. The antimicrobial agent and duration of therapy should be selected based on the host status including presence of complicating conditions, the identity and susceptibility pattern of the pathogen (whether directly determined or extrapolated from aggregate statistics), and the agent's cost and potential side effects [13, 14]. Uncomplicated cystitis can usually be treated with a short course of antibiotics, whereas complicated or invasive UTIs often are more difficult to eradicate and require more aggressive antibiotic therapy, as well as evaluation and treatment of underlying urologic abnormalities or medical conditions [6].

Lower UTI – Cystitis

Epidemiology

Acute bacterial cystitis is a commonly encountered health problem, accounting for over 5 million visits to physician offices and over $1 billion in medical costs annually in the United States [2]. Uncomplicated cystitis is defined as an infection of the bladder, usu-

Table 1. Factors Suggestive of Increased Likelihood of Complicated or Invasive UTI

Demographics	Male sex, age < 18 or > 65 years, pregnancy
Symptoms	Duration of > 7 days Rigors, flank pain, fever > 101°F (38.3 °C), or other symptoms suggestive of pyelonephritis or bacteremia
Risk factors	Urinary catheterization or recent urologic surgery/instrumentation Obstruction or anatomic defects of urinary tract; functional defects (neurogenic bladder, reflux) Diabetes, sickle cell anemia, immunosuppression (steroids, chemotherapy, HIV infection) Renal insufficiency, polycystic kidney disease, renal transplantation Recent hospitalization or residence in nursing home
Past history	History of childhood UTI 4 ≥ UTIs in past year or pyelonephritis within past 3 months Failure of antibiotic treatment for UTI in past 1 – 3 months

ally bacterial, in an otherwise healthy young woman with normal urinary tract anatomy and renal function. Nearly one-half of women suffer an episode of cystitis during their lifetime. Risk factors for cystitis include female gender, sexual activity, history of previous UTI, use of spermicide-diaphragm contraception, postmenopausal state, and possibly being a nonsecretor of blood group substances [15]. Vaginal colonization with *Escherichia coli* (which normally is absent from the vagina) is promoted by sexual intercourse and the use of spermicide-diaphragm contraception [16]. Spermicides are more toxic to the normal lactobacillus-based premenopausal vaginal flora than to *E. coli*, facilitating overgrowth by *E. coli* [17]. Similar alterations in vaginal flora are also observed in postmenopausal women due to hypoestrogenism [11] and in patients receiving antibiotics, especially β-lactam agents [16]. Some studies indicate that women of the nonsecretor phenotype have a greater risk of recurrent UTI, a higher prevalence of vaginal colonization with gram-negative bacilli, and increased bacterial adherence to vaginal epithelial cells compared to secretor women, possibly because of the expression by nonsecretors' cells of unique receptor glycolipids for P-fimbriated *E. coli* that are not present in the cells of secretor women [3, 16, 18 – 20].

Pathogenesis and Pathology

The vast majority of bladder infections in women are due to ascent of pathogens from the rectum to the vagina and then into the urethra and bladder [3, 4]. In women with uncomplicated cystitis, infection is most commonly caused by *E. coli* (80%), *Staphylococcus saprophyticus* (10 – 15%), and only rarely by other gram-negative bacteria or other organisms [2, 17]. While complicated UTIs still are most often due to *E. coli* (about 50%), they are more likely than uncomplicated cystitis to

involve infection with other gram-negative bacteria including *Klebsiella, Proteus, Pseudomonas, Serratia,* or *Enterobacter*. In addition, *Enterococcus* may be detected, and *Candida* and other yeasts are encountered with increasing frequency. In general, bacteria must have substantial intrinsic virulence to overcome the normal host's urinary tract defenses and cause infection. In contrast, organisms of lesser intrinsic virulence can infect patients with impaired defenses. However, these infections due to less virulent organisms in compromised hosts may paradoxically be more difficult to treat [6].

Manifestations

The clinical syndrome of cystitis is defined by the presence of symptoms localized to the bladder and urethra including frequency, dysuria, and suprapubic pain, without concomitant evidence of renal or systemic involvement. Dysuria due to acute cystitis must be differentiated from that caused by other inflammatory or infectious conditions, including vaginitis, sexually transmitted diseases, and miscellaneous noninflammatory causes of urethral discomfort.

Diagnosis

Bacterial cystitis traditionally has been defined microbiologically by the presence of $\geq 10^5$ colony-forming (CFU) units of bacteria/mL of urine. However, it is now well recognized that UTIs with lower bacterial counts of $10^2 - 10^4$ CFU/mL are responsible for dysuria and frequency in many women [2]. Although a pretreatment urine culture allows for precise targeting of antimicrobial therapy based on the known urinary organisms and their susceptibility patterns, the predictability of the infecting pathogens in cystitis occurring in healthy young women allows such patients to be treated presumptively without a urine culture when the clinical presentation strongly suggests cystitis. Collection of a urine specimen for a quantitative culture before the institution of therapy for UTI is appropriate for patients with complicating factors and in whom pyelonephritis or bacteremia is suspected, and for those who have failed to respond or responded poorly to empiric therapy. Patients recently treated with antimicrobial agents should also usually have pretreatment urine cultures because they are at greater risk of infection with resistant organisms.

Management

Young women with presumed uncomplicated cystitis can often be managed successfully without a traditional physician office visit, e.g. over the telephone or through a clinic by a physician extender who follows a practice guideline. Patients should be screened for risk factors suggestive of a complicated UTI and for evidence of another condition causing the symptoms, especially sexually transmitted disease. If this evaluation is unremarkable, a presumptive diagnosis of uncomplicated cystitis can be made and an empiric trial of antibiotics recommended.

A variety of nonspecific therapies have been advocated for patients with uncomplicated cystitis [21]. Agents to lower the urinary pH, such as hippuric acid or cranberry juice, are usually not necessary and have not been well documented to be beneficial. As an adjunct to antimicrobial therapy for patients with severe dysuria, treatment with oral phenazopyridine (Pyridium) in doses of 200 mg PO TID can provide symptomatic relief.

Table 2. Treatment Options for Uncomplicated Cystitis

Therapy	Comments
Single Dose	
TMP-SMX 2 double-strength (DS) tabs PO	Single dose therapy less effective than 3-day regimen.
Trimethoprim 400 mg PO	Failure of single doses of fluoroquinolones for cystitis due
Ciprofloxacin 250 mg PO	to *S. saprophyticus* is reported.
(or other fluoroquinolones)	
Three-Day Regimens	
TMP-SMX 1 DS tab PO BID	3-day TMP-SMX regimen is a good strategy for most young women with uncomplicated cystitis.
Trimethoprim 100 mg PO BID	Trimethoprim useful in sulfa-intolerant patients.
Ciprofloxacin 250 mg PO BID	Fluoroquinolones useful for patients with complicated UTI
(or other fluoroquinolones)	or those who fail or who are intolerant of TMP-SMX.
Seven-Day Regimens	
As above but continued for 7 days	Indicated for men, diabetics, pregnant women (avoid fluoroquinolones), children (avoid fluoroquinolones), and the elderly, if symptoms present for 7 days, and for other complicated cystitis.

Antibiotic Choice

The choice of antimicrobial therapy for cystitis depends upon the resistance patterns in the local community as well as the underlying host status (Table 2). Knowledge of the antibiotic-resistant patterns in the community or institution, including in nursing homes, should be used to guide the choice of empiric antibiotic therapy while urine culture results.

TMP-SMX is considered by many experts to be the drug of first choice for uncomplicated cystitis because of the low cost and well-established efficacy. Adverse effects may be less frequent with TMP alone, which is a good choice in patients intolerant of sulfonamides. However, in some locales, resistance to TMP-SMX is increasingly prevalent among *E. coli* and other urinary tract pathogens. In these communities, fluoroquinolones may be the preferred agents for empiric therapy. These drugs' excellent spectrum of activity against gram-negative uropathogens and the infrequency of side effects are advantageous. However, the cost of these agents and concerns about the emergence of resistance have lead many to exclude them from consideration as first-line empiric therapy for uncomplicated cystitis. Because of a high prevalence of resistance among uropathogens and their inferior performance in clinical trials, oral first-generation cephalosporins or ampicillin are not generally considered to be first-line therapy for cystitis. However, in cases with confirmed sensitivity, these agents may be reasonable alternatives if TMP-SMX and fluoroquinolones are contraindicated.

Complicated cystitis can be treated initially with fluoroquinolones, which have emerged as drugs of choice in this setting because of their excellent activity against many gram-negative bacteria and their satisfactory per-

formance in clinical trials when compared with traditional intravenous regimens. Subsequent therapy should be guided by the results of urine culture and susceptibility patterns of the identified pathogen.

Duration of Therapy

It is now well recognized that "short course" therapy is adequate for treatment of most women with uncomplicated cystitis. An empiric 3-day course of TMP-SMX or an oral fluoroquinolone is the currently recommended treatment duration [6, 22]. Three-day treatment courses have been well demonstrated to cost less, have fewer side effects, and have comparable efficacy to traditional therapeutic approaches using 7 to 14 days of antibiotics. Single-dose therapy is the most convenient but is associated with higher failure rates than those observed with multiple dose regimens. Longer regimens such as the traditional 7-day regimen are very effective but produce more side effects and should be reserved for high-risk patients. Treatment for a minimum of 7 – 10 days is recommended for UTIs in men, even in the absence of signs of renal or systemic involvement, due to the increased likelihood of undetected underlying complicating factors and the paucity of studies of short-course (3-day) therapy of UTI in men. Men or women known to have complicated cystitis should be treated with a 7- to 14-day course of antibiotics, and even longer periods of therapy may be necessary in selected subgroups.

Prognosis

Complete recovery from cystitis is the norm. Post-therapy urine cultures have traditionally been recommended to confirm successful eradication of infections in patients with acute UTI. However, this is not often necessary in patients with uncomplicated cystitis [1]. In one study, the incidence of symptomatic UTI following therapy for acute cystitis was not reduced when routine follow-up cultures were used (as compared to performing cultures in symptomatic patients only). Post-therapy cultures need to be obtained in nonpregnant women only when there are persisting symptoms or known complicating factors. In contrast, for children, men, pregnant women, patients with obstructive uropathy, or patients with relapsing infection, a follow-up culture should be obtained as a "test of cure".

One challenge for the physician is determining the indications for urologic studies for patients with UTIs. Traditionally, it has been recommended that men with UTIs should be evaluated for predisposing anatomic abnormalities. However, it is now recognized that young men, especially homosexual men and heterosexual men whose female sex partners have vaginal colonization with uropathogens, may develop cystitis in the absence of abnormalities of the urinary tract. In older men, it is certainly still reasonable to screen for prostate abnormalities or neurogenic bladder. More studies are needed to clarify this issue.

Upper UTI – Pyelonephritis

Epidemiology

Pyelonephritis is infection of the renal pelvis and renal parenchyma. Acute bacterial pyelonephritis is one of the most common serious infections of adult women and can also affect children and adult men. In the United States, more than 100,000 patients are admitted to the hospital for an average of 6 – 7 days because of renal infection. The annual risk for hospitalization for pyelonephritis among adults has been estimated at 1 per 1000

women and 0.3 per 1000 men [23]. Many more patients are treated for pyelonephritis as outpatients [24 – 27]. The ratio of pyelonephritis to cystitis episodes has been estimated at approximately 1 : 20 [28]. Increased risk for pyelonephritis is predicted by many of the same factors as for cystitis. In addition, among children, P_1 blood group phenotype is associated with increased risk of pyelonephritis. Pyelonephritis is also more likely in patients with abnormalities of the urinary tract including neurogenic bladder, posterior urethral valves (in infant boys), congenital vesicoureteral reflux (in girls), chronic urinary catheterization, urolithiasis, and kidney transplantation [29 – 32].

Pathogenesis

In most cases, pyelonephritis arises as an ascending infection wherein bacteria enter the urinary tract via the urethra, establish bladder colonization, and then ascend up the ureters to the kidneys [3, 32]. Usually the pathogens are derived from the host's own intestinal, and in women, vaginal, flora [16, 33]. If the patient is catheterized, the urine can be contaminated from the hands of healthcare workers or other environmental sources [34].

The microbial flora of pyelonephritis is quite similar to that of acute cystitis, with *E. coli* accounting for over 80% of cases and other gram-negative bacilli including *Klebsiella* and *Proteus*, as well as *S. saprophyticus* and *Enterococcus* making up the remainder of cases [32]. The *E. coli* strains that cause pyelonephritis are quite distinct from ordinary intestinal *E. coli* and belong to a limited number of genetic lineages characterized by specific antigens and other properties that promote invasion and inflammation within the upper urinary tract [32, 35]. *E. coli* strains that cause pyelonephritis are likely to express adhesins including P fimbriae, which recognize Gal (α1-4) Gal-containing receptors on host epithelial surfaces via their adhesion molecule, PapG. PapG occurs in 3 known variants. Class II variants are the most common among *E. coli* strains that cause pyelonephritis and bacteremic UTIs, whereas class III variants predominate in cystitis. Other virulence factors of *E. coli* include the cytotoxin alpha hemolysin, the aerobactin iron sequestration system, polysaccharide capsules, lipopolysaccharide, and serum resistance proteins [19, 35].

Host factors also can promote ascending infection. Ascent of bacteria up the ureters is more common in patients with vesicoureteral reflux, whether due to underlying congenital or acquired urological abnormalities or secondary to acute changes in ureteral peristalsis induced by irritation of the ureter by lipopolysaccharide from adherent bacteria [32]. Pathogens can move from the renal pelvis into the collecting ducts and tubules due to intrarenal reflux [32]. Pyelonephritis is promoted during pregnancy by physiologic urethral hypotonia and partial ureteral obstruction.

Pathology

Pathogenic bacteria in the urinary tract adhere to the mucosa and trigger inflammation with production of proinflammatory cytokines and influx of polymorphonuclear leukocytes and other inflammatory cells [20]. Reactive oxygen species, leukotrienes, and prostaglandins act in concert with bacterial cytotoxins to produce tissue damage and renal vasoconstriction [19, 32]. The kidney becomes edematous and infiltrated with leukocytes, tubules may become necrotic, and microscopic and macroscopic abscesses may form.

Clinical Manifestations

Patients with pyelonephritis typically present with progressive flank pain, malaise, fevers, and possibly gastrointestinal symptoms of nausea and vomiting. These symptoms of pyelonephritis may be preceded or accompanied by symptoms of acute cystitis such as dysuria, urinary frequency, and urgency. On physical examination, patients are generally more ill appearing than those with simple cystitis. They are febrile and often are dehydrated and tachycardic. Tenderness over the costovertebral angles can be elicited with palpation or percussion. However, atypical presentation of pyelonephritis is not uncommon [36]. Symptoms may localize to the abdomen, pelvis, or back. Patients with sensory impairment may have minimal local symptoms and present solely with fever or hypotension.

Diagnosis

The clinical diagnosis of pyelonephritis is based on characteristic symptoms and signs and supportive laboratory tests [37]. Urinalysis and urine culture with susceptibility testing should be obtained in all patients with suspected pyelonephritis [2]. A gram stain of the urine is particularly helpful in confirming the presence of bacteria and suggesting a likely bacterial type, distinguishing between gram-positive and gram-negative pathogens. In the absence of prior antimicrobial therapy, the urine culture in most patients with pyelonephritis will have $> 10^5$ CFU of bacteria/mL of urine. Antimicrobial sensitivity testing is important and should be used to tailor antibiotic choices when the results are available. Blood cultures will be positive in a large percentage of patients with acute pyelonephritis. Their use in uncomplicated pyelonephritis is considered optional by some experts because bacteremia is usually adequately treated with the antibiotics chosen for the UTI, and clinical outcome is most often independent of blood culture results.

Imaging studies are not routinely needed for the diagnosis or management of acute pyelonephritis [30, 37, 38]. However, in patients who fail to respond appropriately to therapy, further diagnostic studies and interventions are indicated [38]. Suspicion of obstruction or renal abscess should prompt additional evaluation. If obstruction is suspected, abdominal roentgenograms to screen for urinary calculi may be appropriate, followed by excretory urography if indicated. Computed tomography (CT) scanning may provide the best definition of anatomical abnormalities [39]. Contrast-enhanced CT scan facilitates detection of abscesses and allows their differentiation from surrounding inflamed tissue. Streaky or wedge-shaped hypodense areas that fail to concentrate contrast material normally are indicative of pyelonephritis. Other CT findings in pyelonephritis may include a swollen, enlarged kidney, focal bulges of the kidney, and inflammatory stranding in the perinephric fat. Under the new terminology, these CT findings are now labeled as “acute pyelonephritis” by the radiologist, and modifiers are used to describe the specific observed anatomic abnormalities [40]. The extent and severity of the CT findings have been demonstrated to correlate with risk of bacteremia and other complications, including death. Ultrasound is now recognized as less sensitive than CT for detecting or following pyelonephritis but remains useful for detecting perinephric abscesses or obstruction and hydronephrosis. Single photon emission CT (SPECT) scanning using Tc-99m (dimercaptosuccinic) acid (DMSA) is even more sensitive than CT for detecting inflammation but is less useful in differentiating abscesses from inflamed tis-

Table 3. Treatment Options for Pyelonephritis

Entity	Drug	Duration
Subclinical or mild-moderate pyelonephritis (outpatient)	TMP-SMX 1 DS tab PO BID Ciprofloxacin 500 mg PO BID (or other fluoroquinolones)	14 days
Moderate-severe pyelonephritis (inpatient initially)	*Enterococcus:* IV ampicillin ± gentamicin; Gram-negative bacteria: IV fluoroquinolone, third-generation cephalosporin, aztreonam or gentamicin	IV therapy until clinically stable, then complete 14-day course with oral antibiotics
Complicated pyelonephritis	IV broad spectrum antibiotics, usually to include agents active against *Pseudomonas*, especially if nosocomial or nursing home-acquired infection	IV therapy until stable, followed by oral drugs to complete a minimum of 14 days; longer therapy may be necessary.

sues. Nonenhanced spiral CT may be superior to conventional CT or excretory urography for detecting urolithiasis.

Clinical Management

Severity of illness is the main determinant of the need for hospital admission and parenteral therapy in the patient with pyelonephritis [23, 26, 27]. If a reliable patient is clinically stable and able to take oral medications, a trial of outpatient therapy can be considered and can result in significant cost savings [25]. Parenteral therapy is needed for the patient with nausea and vomiting who is unable to take oral medications. If such a patient is otherwise stable, home intravenous (IV) antibiotic therapy may be an option. For the more seriously ill patient, especially if fever, rigors, or unstable blood pressure suggest sepsis syndrome, hospitalization is required. Acute pyelonephritis in the pregnant woman requires hospitalization because of the high risk of bacteremia and potential for significant morbidity and mortality for both mother and baby [23, 41, 42].

Antibiotic Choice

Antibiotic choices for the treatment of pyelonephritis depend upon the severity of symptoms, the causative organisms, and the presence or absence of complicating factors [37, 43] (Table 3). For mild cases of pyelonephritis, outpatient therapy with oral antibiotics such as TMP-SMX or fluoroquinolones in the same doses prescribed for cystitis but continued for 2 weeks may be sufficient. If hospitalization and parenteral therapy are required, options for treatment of uncomplicated pyelonephritis include IV, fluoroquinolones, aminoglycosides, or third-generation cephalosporin drugs (Table 3). If the in-

itial gram stain of the urine culture suggests the possibility of *Enterococcus*, IV ampicillin with or without gentamicin should be considered. Other possible agents include imipenem or other broad-spectrum antibiotics. The choice of antibiotics should be adjusted as indicated by the infecting organism's susceptibility pattern, when available. For hospitalized patients, parenteral antibiotics should be continued until the patient is stable, after which oral antibiotics can usually be used to complete the treatment [6, 43, 44].

Care must be exercised in the choice of antibiotics for pregnant women [6, 45]. Fluoroquinolones should be avoided in pregnant women (and in children) because of concerns about their effect on cartilage development. Aminoglycosides should be used with caution due to the possibility of fetal cranial nerve VIII damage, and TMP-SMX should be avoided near term to avoid kernicterus in the baby. Tetracyclines are contraindicated in children and pregnant women.

Duration of Therapy

The optimal duration of therapy for pyelonephritis has not been well studied. Although treatment for as long as 6 weeks has traditionally been advocated, > 2 weeks of treatment is usually not necessary for uncomplicated cases [46, 47]. Some studies have explored the possibility of reducing the duration of therapy to ≤ 1 week [30, 44], but concern remains that there may be an increased risk of relapse with such a short course of treatment [43]. Fortunately, the availability of oral fluoroquinolones increases the ease of IV to PO switching and again allows earlier discharge from the hospital. Therapy for > 14 days may be necessary in selected cases of complicated pyelonephritis or in men if prostatic infection is suspected.

Prognosis

With appropriate antimicrobial therapy, the prognosis for patients with pyelonephritis is complete recovery. In patients who fail to respond clinically after 72 hours of therapy with appropriate antibiotics, additional evaluation is indicated. Careful review of antibiotic sensitivity based on culture results should be undertaken [48]. Radiographic imaging to rule out obstruction, anatomic abnormalities, or intrarenal or perinephric abscesses can be considered [38]. Renal ultrasound, CT scans and possibly an intravenous pyelogram (IVP) may be necessary to detect abnormalities requiring surgical intervention.

Careful follow-up of patients with pyelonephritis is important, but the specifics of the required evaluation are unclear. At the least, instructions to return if symptoms recur is critical. The role of follow-up office visits, urinalysis, or urine culture is undefined. Follow-up "test of cure" urine cultures should be done within 1 – 2 weeks of completion of therapy in pregnant women, children, and patients with multiple episodes of pyelonephritis, and should be considered for other patients [49].

Complications

The intense renal inflammation associated with pyelonephritis can have functional consequences. Inflammation-induced tubular dysfunction can result in delayed excretion of contrast dyes and, rarely, overt acute renal failure (ARF) [36]. However, these changes usually are not clinically significant or persisting. Pyelonephritis can be complicated by bacteremia, especially during pregnancy and in older patients or those with obstructed urine flow. Septic shock with disseminated in-

travascular coagulation (DIC), adult respiratory distress syndrome (ARDS), and multiorgan failure can occur [43].

Particularly in hyperglycemic diabetic patients, rapid fermentation of glucose by the bacteria can produce gas within the kidney, causing emphysematous pyelonephritis (if the renal parenchyma is involved), gas abscess, or emphysematous pyelitis (if the renal pelvis or collecting system is involved) [50]. Papillary necrosis can also complicate pyelonephritis, especially among diabetics. In this circumstance, infection causes sloughing of the tissue, which can cause obstruction and worsen infection.

Kidney-associated abscesses may be intrarenal or perinephric [51, 52]. They occur predominantly in compromised hosts, especially in patients with diabetes, recent surgery or instrumentation of the urinary tract, or urinary reflux or obstruction. Those abscesses that develop as a complication of pyelonephritis are usually due to a gram-negative bacteria, especially *Enterobacteriacae*. In contrast, staphylococcal abscesses may occur secondary to bacteremia. Indeed, the isolation of *Staphylococcus aureus* in the urine in a febrile patient without urinary tract instrumentation signals the need for investigation of possible associated bacteremia. *S. aureus* abscesses should be treated with antistaphylococcal penicillin drugs or first-generation cephalosporins, whereas abscesses due to gram-negative bacteria should be treated with agents active against these organisms [51, 53]. Small abscesses may respond to medical management, but especially with larger abscesses, surgical or image guided needle drainage may be necessary [54, 55].

Recurrent UTIs

Recurrent infections pose important challenges to the patient's physician [1, 2, 18, 28, 56]. Differentiation between reinfection and relapse is critical to the correct management of these 2 very different conditions [2]. Reinfection implies newly-introduced infection with a new organism. Although such repeat infections are usually due to *E. coli*, the new organisms are different strains of this species. Risk factors for reinfection include sexual intercourse and use of diaphragm/spermicide as contraception [15, 56]. In contrast, relapse implies recurrent infection caused by the same organism, usually beginning soon after completion of an initial course of therapy, and is attributable to incomplete treatment of the initial episode. Relapse is more likely to occur in complicated UTI and is attributable to a persistent nidus of infection. Functional or anatomic abnormalities, prostatitis, or infected stones should be suspected.

Prevention of reinfection is focused on preventing reintroduction of bacteria into the urinary tract (Table 4). Oral antimicrobial therapeutic regimes have been shown to decrease the likelihood of reinfection and recurrent UTI [1, 2, 6]. For reliable patients, patient-initiated antibiotic therapy immediately after the onset of symptoms can be useful. In women who can accurately identify when they are developing a recurrence, a supply of antibiotics, usually TMP-SMX or a fluoroquinolone kept at home and initiated with onset of symptoms, can be effective. If recurrent UTI episodes are related to sexual intercourse, postcoital antibiotic prophylaxis can be helpful [57]. Because diaphragm/spermicide contraception is associated with high risk of urinary tract infection, alternative contraceptive methods should be considered. Continuous

Table 4. Management of Recurrent Cystitis Due to Reinfection

Post-coital prophylaxis	TMP-SMX 1 single-strength or 1 DS tab PO or Nitrofurantoin 50 – 100 mg PO
Continuous prophylaxis (daily or 3 times per week)	TMP-SMX 1 single-strength tab PO or Trimethoprim 100 mg PO or Nitrofurantoin 50 – 100 mg PO
Patient-initiated therapy	As recommended for single dose or 3-day therapy of cystitis

antibiotic prophylaxis can be used in patients with frequent (> 2 – 3 per year) episodes of UTI. Chronic prophylaxis (daily or thrice weekly) with low doses of TMP-SMX or a fluoroquinolone has been demonstrated to reduce the frequency of recurrences from 2 – 3 episodes per year to about 0.2 episodes per year among women with frequent UTI. Such prophylaxis is often continued for 6 months to a year and then interrupted to see if episodes of UTI recur. If so, prophylaxis can be resumed. Fortunately, emergence of resistant strains has not been a significant problem for women using long-term antibiotic prophylaxis for UTI. Finally, postmenopausal women with recurrent UTI may benefit from topical vaginal estrogen replacement therapy [11].

In contrast to reinfection, relapse of UTIs requires investigation of the underlying cause. A urine culture should be obtained and a full 7- to 14-day course of appropriate antibiotics initiated. Diagnostic studies should be considered to search for an occult source of infection in the kidney, perinephric space, or prostate and for urologic abnormalities including anatomic defects [18]. Renal, urethral, or bladder stones and other causes of obstruction need to be ruled out. Urinary tract stones may occur in patients with chronic infection due to a urease-producing organism such as *Proteus mirabilis*. Removal of calculi via lithotripsy or surgery is often necessary before antibiotics can effectively eradicate infection in patients with urolithiasis.

Catheter-associated UTI

Bacteriuria in patients with indwelling catheters occurs at a rate of 3 – 10% per day of catheterization and is nearly universal in patients with prolonged catheter use [58]. Routine treatment of asymptomatic bacteriuria in catheterized patients does not improve survival and often results in the selection of increasingly resistant microbes. Nevertheless, some bacteriuric patients will go on to develop symptomatic cystitis, pyelonephritis, and even bacteremia. Antibiotic therapy should be reserved for catheterized patients with significant symptoms or signs attributable to UTI [34].

Treatment of symptomatic UTI in the catheterized patient should include attempts to remove the catheter plus administration of appropriate antibiotics. Because catheterized patients often have infections due to bacteria other than *E. coli*, urine cultures are desirable to define the pathogen's identity and sensitivity patterns. Urine samples should be obtained directly from the Foley catheter and not from the drainage bag. Choice of initial empiric treatment should be based on review of the

organisms known to have previously infected the patient and on resistance patterns in the hospital or nursing home. TMP-SMX or fluoroquinolones are often reasonable choices until culture and sensitivity results are available, at which time therapy should be modified as needed. By definition, catheter-related infections are complicated UTIs, and antibiotics should be continued for ≥ 7 days.

Prevention of UTIs in catheterized patients is desirable but difficult [2]. The best preventive method is to avoid unnecessary use of urinary catheters. Use of diapers or pads, external drainage devices, or possibly intermittent catheterization is preferable to chronic catheterization [59]. Clean technique, as opposed to sterile technique, has been shown to be adequate for patients trained in self-administered intermittent catheterization [58]. Antibiotic prophylaxis may be useful for the patient with short-term catheterization [6], but this remains controversial. However, routine antimicrobial prophylaxis should not be used for chronically catheterized patients [2, 60]. This approach serves only to select antibiotic-resistant organisms [58, 60]. If chronic indwelling catheters must be used, meticulous handwashing by all caregivers should be emphasized. The role of local antibiotics and antibiotic impregnated catheters remains incompletely defined [2, 6, 61]. Reflux of urine from the collecting system into the bladder and breaks in the drainage system must be avoided.

The patient with neurogenic bladder and recurrent UTIs poses a particular challenge [62]. Intermittent catheterization or, in men, condom drainage with or without sphincterotomy can be useful. The use of alpha-blockers to control autonomic dysreflexia or of anticholinergic agents to improve incontinence should be considered. Transurethral sphincterotomy and external drainage may be needed to maintain low voiding pressures. Diversion procedures are required for some patients but are becoming less popular because of a variety of complications [62].

UTI in Children

In children, both asymptomatic bacteriuria and symptomatic UTIs should be treated with antibiotics, with drug choice determined by the results of urine culture [29, 31, 63]. Low bacterial counts in urine cultures from infants may reflect infection requiring treatment [64]. Short-course therapy is not appropriate, and antibiotics should be continued for 7 – 14 days. TMP-SMX is often appropriate as empiric therapy, and the acutely ill child with suspected pyelonephritis should receive treatment with parenteral antibiotics pending culture results [65]. Cure should be documented by follow-up urine cultures [29].

In many children, especially infants, UTIs should prompt diagnostic imaging because of the likelihood of discovering anatomic or functional urinary tract abnormalities and the high risk of renal damage from infection [18, 29, 30, 66, 67]. Ultrasonography is a commonly used initial test. A voiding cystourethrogram (VCUG) can be used to look for evidence of reflux in young children and in children with an abnormal ultrasound or a history suggestive of voiding dysfunction [30, 66]. Children found to have reflux should be placed on suppressive antibiotics at least until 5 years of age and have regular urine evaluations for unexplained febrile illnesses, with aggressive treatment of identified UTIs [31]. Surgical interventions are clearly required for obstructive lesions and may be considered in the child with reflux who develops recurrent UTI despite antibiotic therapy [66].

UTI after Renal Transplantation

Renal transplant recipients are at high risk for renal infection, both for mechanical reasons and because of the immunosuppressive therapy used to prevent graft rejection. Continuous prophylactic antibiotic therapy with TMP-SMX is commonly used in this context. Such therapy additionally provides protection against opportunistic infections such as nocardiosis, toxoplasmosis, or *Pneumocystis carinii* pneumonia, for which these patients are at risk. The efficacy of continuous TMP-SMX prophylaxis in preventing UTI and bacteremia in kidney transplant recipients was documented in a recent trial using both a standard dose (160 – 400 mg daily) and a higher dose regimen (320 – 800 mg daily). Emergence of resistance was not observed [6].

Prostatitis

Prostatitis syndromes can be divided into 4 types: acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostadynia [68, 69]. The diagnostic approach and therapeutic management differs markedly between these 4 conditions [70].

Acute bacterial prostatitis denotes bacterial infection of the prostate and usually manifests with an abrupt onset of symptoms [68]. The patient classically presents with fevers, dysuria, frequency, obstructive voiding symptoms, and extreme perineal pain. The diagnosis of acute bacterial prostatitis is often quite obvious, with extreme tenderness to palpation of the prostate. Indeed, vigorous prostatic massage should not be performed in these patients because of the risk of precipitating bacteremia. To confirm the diagnosis and an etiologic agent of acute prostatitis, a urinalysis and urine culture should be performed. The urine specimen will usually show significant pyuria and may reveal hematuria. Urine culture will be positive. The most common organisms identified are *E. coli* and less frequently *Enterococcus* and other gram-negative bacilli, including *Pseudomonas*.

Treatment of acute bacterial prostatitis consists of empiric antibiotic therapy followed by tailoring of this therapy based on the results of urine culture and sensitivity patterns. Currently, the drug of choice is considered by many to be a fluoroquinolone, but TMP-SMX is also a reasonable choice. If the patient appears seriously ill with a high fever and the possibility of bacteremia is suspected, hospitalization for treatment with broad-spectrum IV antibiotics and supportive care may be needed. On occasion, prostatic edema can be so severe that acute urinary retention can result. In this case, urologic consultation and treatment with suprapubic urinary drainage catheter is needed. When the patient has been stabilized, antibiotic therapy can be given orally. Acute bacterial prostatitis requires prolonged therapy with oral antibiotics. A minimum treatment duration of 30 days, and sometimes 6 weeks to 3 months, may be required.

Chronic bacterial prostatitis is characterized by relapsing urinary tract symptoms and evidence of prostatic infection [68]. The patient may have prostatic, perineal, or suprapubic discomfort, but the symptoms are usually more intermittent and milder than those observed in acute bacterial prostatitis. Prostatic massage may yield secretions that contain > 10 white blood cells per high power field. The presence of white blood cells in the expressed prostatic secretions but not in the pre-massage urine favors the diagnosis of

chronic bacterial prostatitis rather than recurrent cystitis. Most patients with chronic bacterial prostatitis have infection with a gram-negative bacillus, and the recurrent episodes are caused by the same organism. Treatment involves identification of the infecting organism and long-term (1 – 3 months) oral antibiotic therapy with agents such as TMP-SMX or fluoroquinolones. Some patients with chronic bacterial prostatitis may have prostatic calculi that harbor organisms capable of causing recurrent symptomatic episodes. These patients are particularly likely to require long-term antibiotic treatment to eradicate the infecting organism. Occasionally, transurethral resection of the prostatic gland (TURP) to remove prostatic calculi may be necessary.

Nonbacterial prostatitis is infectious prostatitis for which no identifiable bacterial etiology can be found [71]. Prostatic inflammation is evidenced by the presence of > 10 white blood cells per high power field in expressed prostatic secretions. However, in contrast to bacterial prostatitis, routine cultures of expressed prostatic secretions will be negative. Patients present with symptoms including prostatic, perineal, or suprapubic pain that may be indistinguishable from symptoms of chronic bacterial prostatitis. A variety of organisms have been postulated as possible etiologic agents of nonbacterial prostatitis, including *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma*, and *Trichomonas vaginalis* [72]. However, a definite role for any of these agents has not been established [71]. Nevertheless, many experts will give a trial of antibiotic therapy directed towards these unusual organisms in patients who present with nonbacterial prostatitis. Most commonly, a 2- to 4-week trial of doxycycline or tetracycline is attempted. If the patient experiences symptomatic improvement, it is possible that the antibiotic has treated an infecting organism. However, it may be difficult to distinguish between a placebo effect, coincidental improvement, nonspecific anti-inflammatory actions, and true response to the antibiotic. A variety of non-antimicrobial approaches have also been utilized in the treatment of nonbacterial prostatitis. The use of nonsteroidal anti-inflammatory agents, sitz baths, and avoidance of caffeine or alcohol, which can cause bladder irritation, have been advocated. Some patients may respond to treatment with alpha adrenergic blocking agents such as terazocin.

Prostadynia is a condition that can be quite distressing to the patient and difficult to treat [73]. Patients with prostadynia have symptoms similar to prostatitis but no evidence of infection or inflammation upon examination of urine or expressed prostatic secretions. The etiology of prostadynia is unknown. The role that stress or emotional problems play in the etiology of prostadynia remains to be defined. In some patients, urologic evaluation may reveal obstructive voiding physiology, but the vast majority of these patients will have no abnormalities on urological evaluation. Some patients with prostadynia may benefit from treatment with alpha adrenergic blocking agents [74] or muscle relaxants such as diazepam. Stress reduction and attention to underlying emotional problems contribute to the complete care of the patient [75].

Unusual Infections

Candida UTI

Candida UTI now represents the fourth most common cause of nosocomial UTIs (Table 5). The vast majority of candiduria epi-

Table 5. Treatment Options for Candidal UTI

Therapy	Comments
None	Appropriate in most asymptomatic patients without evidence of dissemination.
Fluconazole	Drug of choice for uncomplicated symptomatic cystitis (200 mg PO q day x 7) or ascending pyelonephritis (400 mg PO or IV q day).
Amphotericin B bladder washes (50 mg/L sterile water administered via triple-lumen catheter for 7 – 14 days)	Alternative for use in symptomatic patient requiring chronic Foley catheterization. No advantage over fluconazole in absence of fluconazole resistance.
Parenteral amphotericin B	Remains the drug of choice for disseminated disease in the immuno-compromised patient, but increasing evidence for efficacy of azole drugs.

sodes originate from the lower urinary tract. *Candida* UTIs may manifest as asymptomatic candiduria, cystitis, pyelonephritis, hematogenous renal candidiasis, or fungus balls [76]. When yeast is identified on urine culture, it is often advisable to determine that it is persistent. If a repeat urine specimen confirms the presence of yeast, it is important to consider the possibility of an underlying cause such as catheterization, prolonged antibiotic therapy, immunocompromising medical conditions, or urinary tract anatomic abnormalities.

If the patient with candiduria is asymptomatic, therapy is rarely appropriate. In the patient with a Foley catheter, it is reasonable to attempt at least one trial of changing or removing the catheter. Asymptomatic candiduria is widely overtreated, and treatment of asymptomatic infection is probably only justified before urologic surgery or manipulation and in the patient at high risk for disseminated fungemia such as the neutropenic host or other immunocompromised individual.

Symptomatic *Candida* cystitis usually should be treated with oral azoles [77]. Local bladder irrigation with amphotericin B is an alternative, particularly in the chronically catheterized patient. Ascending candidal pyelonephritis is an uncommon complication of candidal cystitis and usually only occurs in patients with diabetes and/or urinary obstruction. Instead, renal candidiasis is usually due to hematogenous seeding as a manifestation of disseminated fungal infection. Systemic therapy with fluconazole or amphortericin B is required for renal *Candida* infection irrespective of the route of acquisition. Patients with possible disseminated disease may need additional diagnostic or therapeutic interventions, plus a longer duration of treatment.

Viral UTI

In immunocompetent hosts, viral infections usually do not produce symptoms in the uri-

nary tract. However, in immunocompromised patients, significant manifestations such as hematuria, dysuria, and frequency can be associated with viral UTIs. Viral UTIs have been described as acute illnesses including acute hemorrhagic cystitis in children with adenovirus and in bone marrow transplant patients infected with adenovirus or polyoma virus. Viral UTIs can also occur as part of disseminated viral illnesses such as mumps, cytomegalovirus, measles, or varicella virus.

Tuberculous UTI

Tuberculous involvement of the urinary tract is well described. The pathogenesis of genitourinary tuberculosis (TB) is usually thought to involve hematogenous seeding of the renal cortex with progression to the medulla. Patients with renal TB are often asymptomatic but may present with dysuria or hematuria or, less commonly, with constitutional manifestations of disseminated tuberculosis. Evidence of active TB outside of the genitourinary tract is identified in < 10% of patients with renal TB, but evidence of old pulmonary infection can be found in most patients. Patients with genitourinary TB are often identified when "sterile pyuria", i.e. pyuria with negative routine bacterial cultures, is noted. *Mycobacterium tuberculosis* can be grown from the urine in the majority of cases. Genitourinary TB can be complicated by the development of ureteral strictures, hydronephrosis, and renal parenchymal abscesses. The IVP may demonstrate strictures or a beading pattern in the ureters, and ultrasonography may reveal hydronephrosis or an infiltrative process in the renal parenchyma. Treatment of renal TB is the same as that for other forms of TB.

Non-candidal Fungal UTI

Infection of the urinary tract with a variety of fungi, including cryptococcus, blastomycosis, or histoplasmosis, has been described. Treatment with the new azole drugs may be effective, but amphotericin-B therapy is sometimes necessary.

Parasitic UTI

A variety of parasites can also infect the urinary tract including *Schistosoma haematobium, Schistosoma mansoni*, or *Onchocerca volvulus*. Hematuria is suggestive of infection with *S. haematobium*, and the eggs of this trematode, as well the eggs of *S. mansoni*, can be detected in urine samples. Therapy of parasitic infections should be tailored to the specific organism.

The Dysuric Patient

Many conditions may cause the patient to present with dysuria [2]. About one-half of young women with dysuria will have classical bacterial cystitis with > 10^5 CFU of bacteria/mL urine on culture. In the remaining patients who have what has been termed "urethral syndrome", symptoms are due either to bacterial cystourethritis with fewer organisms or to other conditions. Bacterial cystitis must be distinguished from sexually transmitted diseases, vaginitis, and noninfectious etiologies of dysuria. Urethritis may be caused by genital *Herpes simplex* virus, *Chlamydia trachomatis*, gonorrhea, or other sexually transmitted diseases. *Candida* or *Trichimonas* vaginitis often presents with dysuria. Patients with *C. trachomatis*, gonorrhea, *Candida*, or

Trichimonas will respond to appropriate antimicrobial therapy for these conditions. Hypoestrogenism, urethral spasm, or chemical irritation can produce dysuria in the absence of infection. Finally, approximately 10% of patients with dysuria-frequency syndrome have no evidence of infection or any other identifiable cause for their symptoms.

Summary

Optimal management of acute UTI requires delineation of the patient's clinical syndrome and consideration of the underlying host status followed by selection of an antimicrobial agent and duration of therapy appropriate to the clinical situation. The choice of antimicrobial agent should be guided by the susceptibility pattern of the infecting organism and relevant characteristics of the antimicrobial agent, including efficacy, cost, pharmacokinetic properties and adverse effect profile. For women with uncomplicated cystitis, short-course therapy with 3 days of TMP-SMX or a fluoroquinolone is optimal. In other clinical situations, including complicated cystitis, pyelonephritis, prostatitis or bacteremic UTIs, longer courses of therapy are indicated. Pretreatment urine cultures are not necessary in most young women with uncomplicated cystitis but should be used to guide therapy in most other circumstances. Asymptomatic bacteriuria requires treatment only in children, pregnant women, and patients undergoing urinary tract instrumentation likely to be associated with bacteremia. Urologic investigation is warranted in patients not responding to therapy for UTI, when obstruction is suspected, with relapse of infection due to the same strain of bacteria and in children with symptomatic UTI, but not in the vast majority of women with uncomplicated UTI. Unusual organisms may cause UTI and should be considered based on historical or other clinical clues.

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