Clinical Presentations and Epidemiology of Urinary Tract Infections

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ABSTRACT Urinary tract infection (UTI) is one of the most common bacterial infections, and the incidence in women is much higher than in men. The diagnosis of a UTI can be made based on a combination of symptoms and a positive urine analysis or culture. Most UTIs are uncomplicated UTIs, defined as cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract, and does not exhibit signs of tissue invasion and systemic infection. All UTIs that are not uncomplicated are considered to be complicated UTIs. Differentiation between uncomplicated and complicated UTIs has implications for therapy because the risks of complications or treatment failure are increased for patients with a complicated UTI. Asymptomatic bacteriuria (ASB) is defined as the presence of a positive urine culture collected from a patient without symptoms of a UTI. Concerning the complicated UTI, it is possible to make a differentiation between UTI with systemic symptoms (febrile UTI) and UTI in a host, which carries an increased risk to develop complications of this UTI. Febrile UTIs are urosepsis, pyelonephritis, and prostatitis. A complicated host is defined as one that has an increased risk for complications, to which the following groups belong: men, pregnant women, immunocompromised patients, or those who have an anatomical or functional abnormality of the urogenital tract (e.g., spinal cord-injury patients, renal stones, urinary catheter).

CLINICAL SYNDROMES AND DEFINITIONS
Urinary tract infection (UTI) is one of the most common bacterial infections. Bacteria live around the urethra and colonize the bladder, but are washed out during micturition. The shorter distance to the bladder in women (as compared to men) makes it easier for bacterial colonizers to reach the bladder. Furthermore, the urethral opening in women is close to the rectum. Urogenital manipulations associated with daily living or medical interventions facilitate the movement of bacteria to the urethra (1).

The diagnosis of a UTI can be made by a combination of symptoms and a positive urine analysis or culture. In most patient groups, the threshold for bacteriuria is considered to be 1,000 colony-forming units (cfu)/ml, based on studies correlating midstream-urine specimens with catheterized collection to demonstrate bladder bacteriuria. However, up to 20% of women with classical urinary symptoms can have negative cultures, depending on the cut-off value used (1).

The differentiation between uncomplicated and complicated UTIs has implications for therapy because the risks of complications or treatment failure are increased for patients with a complicated UTI. In general, the following definitions are used: an uncomplicated UTI is an episode of cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract (e.g., spinal cord-injury patients, renal stones, urinary catheter).
All UTIs that are not uncomplicated are considered to be complicated UTIs (2). Therefore, episodes of acute cystitis occurring in healthy nonpregnant women with no history suggestive of an abnormal urinary tract are generally classified as uncomplicated, whereas all others are classified as complicated (3). This distinction has been used to guide the choice and duration of antimicrobial treatment, with broader-spectrum agents and longer courses of treatment often recommended for persons with complicated UTIs. However, this classification scheme does not account for the diversity of complicated UTIs. A classification scheme that stratifies patients with UTI into multiple, homogeneous categories has been proposed but is not (yet) routinely used in practice (2, 3).

Another differentiation of UTIs is between community- and hospital-acquired UTIs. UTIs in patients acquired within the hospital or hospitalized for treatment are generally complicated UTIs. More often uropathogens other than *Escherichia coli* are the causative microorganisms. Furthermore, more-resistant pathogens are cultured compared to community-acquired UTI. Earlier antimicrobial treatment remains the strongest predictor for resistant causative microorganisms (4). Epidemics of nosocomial UTI have been described by recognizing unusual antibiotic-resistance profiles. Most are caused by transmission of outbreak strains between patients on the hands of hospital staff. An estimated 80% of the hospital-acquired UTIs are associated with catheters (1). In a recent study, patients with healthcare-associated (not hospital) UTI were older, had more co-morbidities, and had received previous antimicrobial treatment more frequently compared to patients with community-acquired UTI. Extended-spectrum beta-lactamase (ESBL) *E. coli* and *Pseudomonas aeruginosa* infections were also more frequently cultured (5). Therefore, patients from nursing homes can be considered as having hospital-acquired UTIs.

**Asymptomatic Bacteriuria**

Asymptomatic bacteriuria (ASB), which is defined as the presence of a positive urine culture with at least $10^5$ cfu/ml collected from a patient without symptoms of a UTI, is a common, but usually benign, phenomenon, especially in women (6). Both host and bacterial factors influence the probability that ASB will resolve spontaneously or progress to symptomatic UTI.

A Swedish study among 116 schoolgirls with ASB showed that at baseline renal parenchymal reduction was found in 10.3%, while reflux was found in 20.7%, but only 30% of the 116 patients had a history referable to an earlier UTI. A 3-year follow-up of these 116 schoolgirls with ASB (treated or untreated) showed that the risk of developing renal damage as a result of ASB in a schoolgirl with a roentgenographically normal urinary tract seemed to be small (7).

Long-term follow-up studies have shown that ASB with *E. coli* is not associated with a decline in renal function or the development of end-stage renal failure in a population of generally healthy adult women (8). Although *E. coli* bacteriuria may increase the risk of future hypertension, the pathogenesis is not fully understood (8, 9).

Following the guidelines, screening and treatment is only recommended for pregnant women, or for patients prior to selected invasive genitourinary procedures (6). Clinical trials in spinal cord-injury patients, diabetic women (10), patients with indwelling urethral catheters, and elderly nursing-home residents have consistently found no benefits with treatment of ASB. Negative outcomes with antimicrobial treatment do occur, including adverse drug effects and reinfection with organisms of increasing resistance (11).

In renal-transplant patients, no differences in renal-function prognosis between patients with and without ASB following kidney transplantation could be demonstrated. However, the incidence of pyelonephritis was much higher in the group of patients with ASB. Therefore, screening protocols may be beneficial in this patient group (12).

Since nearly all studies on ASB are performed in women, it is not possible to draw conclusions about the association between ASB, the incidence of UTIs, or the development of renal-function decline in men.

**Uncomplicated Urinary Tract Infection/Cystitis**

Cystitis (infection of the bladder or lower UTI) has the following symptoms: dysuria with or without frequency, urgency, suprapubic pain, or hematuria. Women with a suspected uncomplicated UTI mostly present to primary care. The most-common symptom is urinary frequency. Dysuria is also common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria and when the onset of symptoms is sudden or severe, without the presence of vaginal irritation and discharge (13, 14). Many women also feel extremely unwell and have restricted physical activity. Patients without adequate treatment, in other words, those not given antibiotics, and those with antibiotic-resistant organisms, complain of at least one symptom that is moderately severe or worse lasting for five days (15).
The probability of cystitis is greater than 50% in women with any symptoms of UTI and greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation (3, 13). Therefore, additional urine analysis is not always needed in this patient group.

Acute uncomplicated cystitis rarely progresses to severe disease, even if untreated. A trial with nitrofurantoin and placebo showed that the result for combined symptomatic improvement and cure after three days was present in 27 of the 35 women in the nitrofurantoin group, but also in 19 of the 35 patients in the placebo group. In the same study, only one case in the placebo group (1/38 = 12.6%) progressed to pyelonephritis (16). Therefore, the primary goal of treatment is to ameliorate symptoms. After start of treatment, the symptoms of a lower UTI resolved quickly; the mean duration of urinary frequency was 3.46 days, for hematuria 1.88 days, and for urgency 3.6 days (15).

In 2011, the Infectious Diseases Society of America (IDSA) updated its guidelines for antimicrobial treatment in acute uncomplicated cystitis in women. It is interesting, in view of the worldwide problem of increasing antimicrobial resistance, that these guidelines recommend that ecological adverse effects of an antimicrobial agent (selection for antimicrobial-resistant organisms) must also be considered together with efficacy in selecting the choice of the antimicrobial agent and duration of therapy (17).

Complicated Urinary Tract Infections

It is possible to differentiate between UTI with systemic symptoms and UTI in a host, which has an increased risk to develop complications (complicated host). Systemic symptoms can be noticed by signs of tissue invasion, like fever, flank pain, and delirium. These UTIs can be called febrile UTI, because it is difficult to differentiate between urosepsis, pyelonephritis, and prostatitis (18). However, all of these syndromes require a therapeutic antibiotic drug level in both tissue and urine.

A complicated host is defined as one that has an increased risk for complications of the UTI, to which the following groups belong: men, pregnant women, immunocompromised patients, or those who have an anatomical or functional abnormality of the urogenital tract (e.g., renal stones, urinary catheter, neurogenic bladder, spinal cord injury, renal transplant). Treatment of a UTI (cystitis) in a complicated host requires a therapeutic antibiotic drug level in the urine only, but generally a longer treatment duration is recommended. These different “complicated” hosts are described below in the section Special patient groups.

Urinary Tract Infections with Systemic Symptoms or Febrile UTI

Acute pyelonephritis

Typical clinical manifestations suggestive of pyelonephritis (infections of the kidney or upper UTI) are fever (temperature >38°C) and chills, mental confusion as a sign of delirium, flank pain, costovertebral-angle tenderness, and nausea or vomiting (13, 14). The two routes by which bacteria can invade and spread within the urinary tract are the ascending route and the hematogenous route. There is no clear evidence for a lymphatic route. In practice, nearly all upper UTIs are caused by the ascending route from the bladder to the kidney. Although some patients can remember recent symptoms of cystitis or these symptoms are still present, this is often not the case. It should be recognized that symptoms may vary greatly. Flank tenderness may be more intense when an obstructive disease is present. Normal kidney function can be present, but progressive destruction of the kidney may give rise to clinical manifestations of renal insufficiency.

Prostatitis

Prostatitis ranges from a straightforward clinical entity in its acute form to a complex, debilitating condition when chronic. Diagnosis of acute and chronic bacterial prostatitis is primarily based on history, physical examination, urine culture, and urine-specimen testing. Patients with acute prostatitis complain of symptoms associated with lower UTI, such as frequency and dysuria. They may also experience lower urinary-tract obstruction due to prostatic edema. Therefore, the differential diagnosis of prostatitis includes (amongst others): acute cystitis, benign prostatic hyperplasia, urinary-tract stones, and bladder cancer. On physical examination, patients may have a high temperature and lower abdominal or suprapubic discomfort due to bladder infection. The rectal examination shows an exquisitely tender prostate on palpation (19, 20), but a normal rectal examination cannot exclude this diagnosis (21).

Urosepsis

Urosepsis is defined as sepsis caused by infection of the urinary tract. In urosepsis (as in other types of sepsis), the severity of sepsis mainly depends on the host response. The underlying UTI is almost exclusively a complicated one with involvement of parenchymatous urogenital organs (e.g., kidneys, prostate). The leading cause for developing an uroseptic shock in urological patients is urinary obstruction. It is reported that 17% of patients develop urosepsis after urological interventions (22).
SPECIAL PATIENT GROUPS

Children

UTI is one of the most common bacterial infections in children. UTI in young children and infants are often presented with nonspecific clinical signs, such as fever, irritability, and vomiting, making the diagnosis difficult. Urine collection and interpretation of urine tests in children is not easy and does not always lead to unequivocal confirmation of the diagnosis. Failure to diagnose UTI or delaying treatment of a UTI may result in a clinical deterioration with additional long-term renal damage. Renal anatomical abnormalities that are frequently associated with UTIs are vesicoureteric reflux, double systems, hydronephrosis, hydrourereter, and urethral obstructions (23, 24).

In a cohort study, encopresis was found to be significantly associated with recurrent UTI (25). Therefore, dysfunctional elimination syndromes and constipation should be treated in infants and children who have had a UTI.

Concerning treatment duration, in 10 randomized controlled trials with 625 children with cystitis (aged 3 months to 18 years), no significant differences were found in persistence of clinical symptoms or bacteriuria, recurrent UTI, compliance with medication, or development of bacterial resistance between short duration (2–4 days) oral antibiotic treatment and the earlier-recommended treatment duration of 7–14 days (26).

Men

As a rule, a UTI in a man is considered to be a complicated UTI because the prostate is often involved (21). However, in general, men with a bacterial UTI can be separated into three groups, each with its own therapy:

1. Young men with a UTI without systemic symptoms, where the patient’s medical history and physical examination do not suggest a causative factor. The UTIs in this group can be considered uncomplicated UTIs, but are very uncommon (27).
2. Men with a UTI and systemic symptoms or with a medical history and physical examination that suggest a causative factor. These UTIs must be considered complicated UTIs. The systemic symptoms indicate invasion of the tissue in the prostate (acute bacterial prostatitis) or the kidney (pyelonephritis) (28).
3. Men with complaints that fit a chronic bacterial prostatitis. In these cases, it is advised to wait for the results of the culture. For men with a chronic bacterial prostatitis, a fluoroquinolone is recommended as first choice because these drugs are more effective than trimethoprim/sulfamethoxazole (28, 29). Since it is not an acute illness, the results of the culture (urine, if necessary, after massage of the prostate or semen) can be awaited before therapy is initiated.

Pregnant Women

ASB occurs in 2 to 10% of pregnant women (6). ASB during pregnancy can lead to serious complications for both mother and child. The incidence of ASB is similar in both pregnant and nonpregnant women (30). However, pregnant women with ASB more often develop pyelonephritis, probably due to the anatomic and physiologic changes that occur during pregnancy, which may facilitate bacterial growth and the ascent of bacteria to the kidneys (31). If left untreated, 20 to 40% of pregnant women with ASB will develop pyelonephritis (30, 32, 33). Furthermore, during pregnancy there is an elevated risk of a more severe course of a UTI with adverse consequences for mother and child (34).

Other possible adverse effects, such as preterm delivery and delivering a low-birth-weight infant, are less well established. Although preterm delivery is the main cause of neonatal mortality and morbidity worldwide, the causal mechanisms remain unknown. One of the hypotheses is that endotoxins released by bacteria cause uterine contractions leading to preterm delivery.

Antibiotics are effective again ASB during pregnancy and lower the incidence of pyelonephritis as well as prematurity and dysmaturity (35, 36).

In view of the lack of reported teratogenic effects and the resistance percentages of the causative microorganisms, the beta-lactam antibiotics are a good choice for the treatment of a UTI during pregnancy. Amoxicillin-clavulanic acid or nitrofurantoin are first-choice drugs for the treatment of cystitis during pregnancy (however, nitrofurantoin must not be used just before delivery). In view of the high resistance percentage of the uropathogens for amoxicillin, this drug is not suitable for empirical treatment. A 2nd or 3rd generation cephalosporin is the drug of first choice and amoxicillin-clavulanic acid is second choice for treatment of a pyelonephritis during pregnancy (34).

It is a sign of maternal colonization with group B streptococcus (GBS) whenever a GBS is found in the urine culture. Intravenous-antibiotic treatment of the mother during delivery reduces the number of neonatal infections with GBS (37). Based on the literature, it is recommended that pregnant and nonpregnant women...
with cystitis should be treated for 3–7 days (36). In general, it is recommended to hospitalize a pregnant woman with a pyelonephritis and to administer antibiotics intravenously. After a fever-free period of 24–48 hours, oral antibiotics can be given; the total duration of therapy must be at least 10 days (38).

Patients with a Urinary Catheter
Catheter-associated (CA) infection refers to infection occurring in a person whose urinary tract is currently catheterized or has been catheterized within the past 48 hours. UTI refers to significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternative source. Bacteriuria is a non-specific term that refers to UTI and ASB combined. In the urinary-catheter literature, CA-bacteriuria is mainly comprised of CA-ASB (39).

Indwelling urinary catheters are widely used in hospitalized patients for patients with urinary retention and for frequent monitoring of urine output in critically ill patients. Most patients are catheterized for 2–4 days, but many have a catheter inserted for a longer duration as, for example, spinal cord-injury patients. Unfortunately, the use of indwelling catheters is not without risks. Many catheterized patients develop bacteriuria, with an incidence of 3 to 10% per day (40). Duration of catheterization is the most important risk factor for the development of CA-bacteriuria; almost all patients with long-term catheterization (>1 month) will have bacteriuria. Although most patients with bacteriuria are asymptomatic, symptoms of UTI will develop in some patients. UTI is one of the most common hospital-acquired infections, and 80% of these are associated with the use of indwelling catheters (41). A surveillance study in the Netherlands found that 1.2% of all hospitalized patients had a catheter-associated UTI (42). In a prospective study, the incidence of UTI was 15.6% in about 1,500 patients catheterized for at least 24 hours (43). The proportion of patients with catheter-related bacteriuria in whom symptomatic UTI and bacteremia will develop was estimated through quantitative synthesis of previous reports. Of patients who had indwelling catheters for 2–10 days, bacteriuria was expected to develop in 26%, bacteriuria and symptoms of a UTI would develop in 24%, and bacteremia from a urinary-tract source would develop in 3.6%. Each episode of symptomatic UTI infection was expected to cost an additional $676 US, and catheter-related bacteremia was at least $2,836 US. Given the clinical and economic burden of catheter-related UTI, all health care workers should try to reduce this common complication (44).

In addition to bacteriuria and CA-UTI, long-term catheterization can also lead to the following complications: bacteremia, catheter obstruction, renal and bladder stone formation, incontinence, and, with prolonged use, bladder cancer (39, 45).

The insertion of an indwelling catheter increases the susceptibility of a patient to UTIs, as it provides easier access of microorganisms to the urinary tract. Most of these uropathogens are fecal or skin bacteria from a patient’s own native or transitory microflora. Bacteria can enter the bladder at the time of catheter insertion, through the catheter lumen, or along the catheter-urethral interface. Most microorganisms that cause CA-UTI enter the bladder extraluminally by ascending along the catheter-mucosa interface and are primarily endogenous. Microorganisms can also enter the bladder intraluminally, by contamination of the collecting tube or drainage bag. These organisms are often exogenous, derived from cross-contamination of organisms on the hands of healthcare personnel (39, 40, 46).

Indwelling catheters facilitate colonization of uropathogens by enhancing microbial adhesion. The catheter provides an attachment surface for bacterial adhesins that recognize host-cell receptors on the surfaces of the host cell or catheter. In addition, urinary catheters may damage the uroepithelial mucosa, which leads to exposure of new binding sites for bacterial adhesins. Once attached to the catheter surface or uroepithelium, bacteria undergo phenotypical changes, replicate, and form microcolonies that eventually mature into biofilms. These biofilms protect uropathogens from antimicrobials and the host-immune response, and migrate over the catheter surface to the bladder within 1–3 days. Bacteriuria in patients with short-term catheterization is commonly caused by a single organism, mostly E. coli, while infections in long-term catheterization are polymicrobial (39, 40, 46). Bacteriuria contains a large reservoir of antimicrobial-resistant organisms and can be a source of cross-infection. The most effective way to reduce CA-UTI is to avoid urinary catheterization (39).

The guidelines of the IDSA define CA-UTI as the presence of symptoms: new-onset or worsening of fever, rigors, altered mental status, malaise, or lethargy of no other identified cause; flank pain; costovertebral angle tenderness; acute hematuria; or pelvic discomfort, and more than 1,000 cfu/ml of one or more bacterial species (39).

Results of studies included in a Cochrane review on short-term urinary-catheter use in female patients with abdominal surgery and a urethral catheter for 24 hours, show weak evidence that antibiotic prophylaxis, compared to giving antibiotics when clinically indicated,
reduced the rate of symptomatic UTI [relative risk (RR) 0.20 (95% confidence interval [CI] 0.06–0.66)]. There was also limited evidence that prophylactic antibiotics reduced bacteriuria in nonsurgical patients (47).

Regarding the question as to whether antibiotic prophylaxis is better than giving antibiotics when clinically indicated (i.e., having a symptomatic UTI), the available evidence is too limited to be a basis for clinical practice (39). For patients using intermittent catheterization, the data were inconclusive. For patients using indwelling urethral catheterization, only a single crossover trial with 34 elderly inpatients investigated this issue and results showed fewer episodes of symptomatic UTI in the prophylaxis (norfloxacin) group (48). For patients using intermittent catheterization, the limited evidence suggested that antibiotic prophylaxis reduces the number of episodes of bacteriuria (asymptomatic and symptomatic). For patients using urethral catheterization, no data were available (47). Based on these observations, the contradictory results, and the concerns about rising antimicrobial resistance, prophylactic antimicrobials are not routinely recommended for catheter placement, removal, or replacement. This recommendation is also supported by the low rate of serious complications in the large number of patients undergoing long-term intermittent catheterization with a clean technique in the setting of chronic bacteriuria (39).

CA-UTIs are often polymicrobial and caused by multiple-drug-resistant uropathogens. Urine cultures are recommended prior to treatment in order to confirm that an empiric regimen provides appropriate coverage and to allow tailoring of the regimen based on antimicrobial susceptibility data (39).

Only a few small studies have investigated which causative uropathogens are present in patients with CA-UTIs. The numbers are too small to translate the results into a strong recommendation for empirical treatment. In patients on long-term catheterization, empirical treatment with fluoroquinolones or gentamicin may be warranted to cover less-common microorganisms such as Serratia, Providencia, and Acinetobacter. However, a study from the Netherlands demonstrated that patients with a urinary catheter are at increased risk to have a fluoroquinolone-resistant microorganism (4), which only leaves the toxic aminoglycosides for empirical treatment in this patient group. Earlier antimicrobial treatment remains the strongest predictor for resistant causative microorganisms (4). Therefore, in a patient with a catheter who has only local symptoms and exhibits no signs of a systemic infection, we recommend to wait for the results of the cultures.

It is desirable to limit the duration of treatment, especially for milder infections and infections that respond promptly to treatment, to reduce the selection pressure for drug-resistant flora, especially in patients on long-term catheterization. Therefore, 5–7 days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and 10–14 days is recommended in those with a delayed response, irrespective of whether or not the patient remains catheterized (39).

**Diabetes mellitus**

Diabetic patients have an increased risk for UTI (49, 50). A recent study in primary care patients from the Netherlands demonstrated that relapses and reinfections were reported in 7.1% and 15.9%, respectively, of women with diabetes mellitus (DM) versus 2.0% and 4.1%, respectively, of women without DM. There was a higher risk of recurrent UTI in women with DM compared to women without DM (odds ratio [OR] 2.0; 95% CI 1.4–2.9). Women who had had DM for at least 5 years (OR 2.9; 95% CI 1.9–4.4) or who had retinopathy (OR 4.1; 95% CI 1.9–9.1) were at risk of recurrent UTI (51). This increased recurrence rate was confirmed in one study (52) but not in another (53). In an American study in women with DM type 1 it was found that sexual activity, rather than measures of diabetes control and complications, was the main risk factor for UTI (54).

Diabetic patients more often develop complications, such as bacteremia (55) and a longer hospitalization (50, 56), of their UTI compared to nondiabetic patients. For this reason, cystitis in a patient with DM is considered a complicated UTI.

No prospective trial has investigated the optimal treatment (agent and duration) in these patients. Concerning the recurrence rate of UTI in diabetic compared to nondiabetic women, two studies using Dutch registration databases containing pharmacy-dispensing data from two different time periods show contradictory results (57, 58). In the largest study (58), the prescriptions of 10,366 women with diabetes and 200,258 women without diabetes were compared. Women with diabetes more often received a long treatment, but still had a higher recurrence rate of UTI, compared with those without diabetes.

It is reported that ASB in women with DM is benign and that 20% of diabetic subjects with ASB remained bacteriuric with the original infecting organism throughout the period of observation. Women infected with gram-negative organisms were more likely to have per-
sistent bacteriuria. Many women with resolution of initial bacteriuria, with or without antibiotics, became bacteriuric again during follow-up. Furthermore, ASB in women with DM does not result in renal function decline (59). However, more women with ASB will develop a symptomatic UTI compared to those without (60). Also, in another study with male and female patients with DM type 1 and 2, the presence of ASB was associated with an increased risk of hospitalization for urosepsis (61).

In the above-mentioned prospective study (59), because no evidence was found that ASB alone can lead to a decline in renal function (in women with type 1 and type 2 DM), it is unlikely that treatment of ASB will lead to a decrease in the incidence of diabetic nephropathy. This is in accordance with a study on women with DM and with ASB, in which a comparison was made between women who received antibiotic therapy and women who received placebo. In that study, no difference was seen in serum creatinine levels after a mean follow-up of 2 years (10).

Treatment of ASB in patients with DM is not needed, because in these women ASB does not result in renal function decline, and most of these women do not develop a symptomatic UTI. Therefore, screening for ASB is not indicated in these patients. This is in accordance with the IDSA guideline for the diagnosis and treatment of ASB in adults (6).

RISK FACTORS
Risk factors for uncomplicated and recurrent cases of lower and upper UTI include sexual intercourse, use of spermicides, previous UTI, a new sex partner, and a history of UTI in a first-degree female relative (3, 62–65).

Case-control studies have shown no significant associations between recurrent UTI and precoital- or postcoital-voiding patterns, daily beverage consumption, frequency of urination, delayed-voiding habits, wiping patterns, tampon use, douching, use of hot tubs, type of underwear, or body-mass index (65); however, at least some of this absence of findings might reflect a misclassification of behaviors (3, 66).

A genetic predisposition to recurrent UTI is suggested by the strong association between a history of UTI in one or more first-degree female relatives and an increased risk of recurrent UTIs (63). Certain toll-like-receptor polymorphisms and other genetic variations, particularly those affecting the immune response, are associated with an increased risk for UTI (66, 67). Other studies have shown that acute pyelonephritis was more common in the family members of children with a history of acute pyelonephritis (15%) than in relatives of control subjects (3%) (68).

RECURRENT URINARY TRACT INFECTIONS
Recurrent UTI is a common health care problem and is defined in the literature by three episodes of UTI in the last 12 months or two episodes in the last 6 months. About 20 to 30% of women who have a UTI will have a recurrent UTI (69, 70).

Looking at the causative microorganism, it was recently demonstrated that uropathogenic E. coli adhere, invade, and replicate within the murine bladder urothelium to form intracellular bacterial communities. The presence of exfoliated intracellular bacterial communities and filamentous bacteria in the urine of women with acute cystitis suggests that this pathogenic pathway, characterized in the murine model, may occur in humans. The findings support the occurrence of an intracellular bacterial niche in some women with cystitis that may have important implications for UTI recurrence and treatment (71).

In general, in men and postmenopausal women, it is recommended to exclude anatomical or functional abnormalities of the urogenital tract as a cause of recurrent UTI. In premenopausal women the yield of most diagnostic procedures is low (72).

There are four patterns of response of bacteriuria to therapy: cure, bacteriologic persistence, bacteriologic relapse, or reinfection. Bacteriologic persistence is the persistence of bacteriuria with the same microorganism after 48 hours of treatment. Relapse is an infection with the same microorganism that caused initial infection and usually occurs within 1–2 weeks after the cessation of treatment. A relapse indicates that the infecting organism has persisted in the urinary tract. Reinfection is an infection after sterilization of the urine. Most of the time there is a change in bacterial species. Reinfection can be defined as a ‘true’ recurrence. Both persistence and relapse may be related to inadequate treatment. It is very important to determine whether recurrent UTIs are relapses or reinfections and to make a differentiation between these patterns, since this has treatment consequences. In a persistent UTI the cause must be evaluated. In a relapse of the UTI, the treatment can be given for a longer period.

The first consideration in prevention is to address modifiable behavioral practices. Other effective strategies are generally considered as antimicrobial or nonantimicrobial. Low-dose antimicrobial therapy remains
an effective intervention to manage frequent, recurrent, acute, and uncomplicated UTI. The antimicrobial may be given as continuous daily or every-other-day therapy, usually at bedtime, or as postcoital prophylaxis (69). Topical vaginal estrogen is a potential intervention to decrease the number of recurrent episodes for postmenopausal women (73).

**EPIDEMIOLOGY**

The self-reported annual incidence of UTI in women is 12%, and by the age of 32 years, 50% of all women report having had at least one UTI (3, 74). In a study of young college women, the incidence of cystitis (lower UTI) was 0.70 episodes per person-year (62). Among young healthy women with cystitis, the infection recurs in 25% of women within 6 months after the first UTI. Although the risk of second UTI is strongly influenced by sexual behavior, women with a first UTI caused by *E. coli* are more likely than those with a non-*E. coli* first UTI to have a second UTI within 6 months (75). In a population-based study with 1,017 postmenopausal women, the incidence of cystitis was 0.07 episodes per person-year (76).

In general, about 50 to 70% of women will have a UTI sometime during their lifetime, and 20 to 30% of women who have a UTI will have a recurrent UTI (69, 70). In certain periods of life (childhood, honeymoon, pregnancy, elderly), an increased incidence of UTI has been described (Fig. 1).

Acute pyelonephritis (upper UTI) is much less common than cystitis. Incidence of pyelonephritis is highest among young women, followed by infants and the elderly population. The annual rates of outpatient pyelonephritis in women and men were 12–13 and 2–3 cases per 10,000, respectively (77). UTIs account for approximately 5 to 7% of all cases of severe sepsis (22).

The prevalence of complaints compatible with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is high with an overall rate of 8.2%, with prevalence ranging from 2.2 to 9.7%. Two studies suggest that about one-third of men reporting prostatitis symptoms had resolution after 1 year (19).

The prevalence of ASB depends on the patient group. Different studies report a prevalence of approximately 1 to 5% among healthy young women, increasing to over 20% in the elderly and 12 to 26% in women with DM. In a systematic review and meta-analysis, in which 22 studies were included, ASB was present in 439 of 3,579 (12.2%) patients with DM and in 121 of 2,702 (4.5%) healthy control subjects. The point prevalence of ASB was higher in both women (14.2% DM vs 5.1% controls) and men (2.3% DM vs 0.8% controls) (78).

The high incidence of UTI results in considerable health care costs. The estimated annual direct and indirect cost of UTI in the USA in 1995 was $1.6 billion (equivalent to $2.3 billion in 2010) (1). A nosocomial UTI necessitates one extra hospital day per patient, resulting in almost 1 million extra hospital days each year in the USA (1).

**SUMMARY**

UTI is one of the most common bacterial infections and the incidence in women is much higher than in men. The diagnosis of a UTI can be made based on a combination of symptoms and a positive urine analysis or culture. Most UTIs are uncomplicated UTIs, defined as cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract, and does not exhibit signs of tissue invasion and systemic infection. All UTIs that are not uncomplicated are considered to be complicated UTIs. Differentiation between uncomplicated and complicated UTIs has implications for therapy, because the risks of complications or treatment failure are increased for patients with a complicated UTI. ASB is defined as the presence of a positive urine culture collected from a patient without symptoms of a UTI. Concerning complicated UTI, it is possible to make a differentiation...
between UTI with systemic symptoms (febrile UTI) and UTI in a host, who has risk factors to carry resistant microorganisms and/or with difficulty in successfully treating the infection. Febrile UTIs are urosepsis, pyelonephritis, and prostatitis. A complicated host is defined as having an increased risk of complications including: men, pregnant women, immunocompromised patients, or those who have an anatomical or functional abnormality of the urogenital tract (e.g., spinal cord-injury patients, renal stones, urinary catheter).

REFERENCES


