

Urinary Tract Infection Syndromes

Occurrence, Recurrence, Bacteriology, Risk Factors, and Disease Burden

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KEYWORDS

- Asymptomatic bacteriuria • Cystitis • Pyelonephritis
- Catheter-associated urinary tract infection

KEY POINTS

- The bladder is continuously invaded by bacteria, which can grow to substantial numbers before spontaneous clearance.
- Host factors, host behaviors, and bacterial characteristics are risk factors for the development of symptoms.
- Urinary tract infection (UTI) occurs more often in females than in males.
- Except during pregnancy, asymptomatic bacteriuria is not a treatable condition.
- Cystitis and pyelonephritis are likely to recur, regardless of age, gender, or treatment.
- The gram-negative rod *Escherichia coli* is the most common cause of UTI in all settings, and is transmitted by person-to-person direct contact and the fecal-oral route.
- The proportion of UTI caused by species other than *E coli* is higher in recurring UTI and hospital-acquired UTI.
- The urinary tract is the most common source of bacteremia caused by *E coli*.

DISEASE DESCRIPTION

Urinary tract infection (UTI), an infection anywhere in the urinary tract (urethra, bladder, ureters, or kidneys) is very common. In 2007 in the United States there were 10.5 million ambulatory visits for UTI, accounting for 0.9% of all ambulatory visits.¹ Almost one-fifth (21.3%) of these visits were to hospital emergency departments. UTI is among the most common primary diagnoses for United States women visiting emergency departments.² Prevalence of UTI is high among inpatients also: in a 2004 survey of symptomatic UTI among 49 Swiss hospitals, UTI was detected in 3.7% of those who had been catheterized for at least 24 hours during their hospital stay, and in 0.9% of those who had not been catheterized.³

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This review defines the major UTI syndromes (**Table 1**), their occurrence and recurrence, bacteriology, risk factors, and disease burden. Although the bacteria that cause UTI are increasingly resistant to antibiotic therapies (reviewed elsewhere in this issue), and modern molecular techniques have made it possible to better characterize the genetic lineages of uropathogens, UTI occurrence and risk factors, with few exceptions, have remained relatively constant.

UTI SYNDROMES AND THEIR OCCURRENCE: ASYMPTOMATIC BACTERIURIA, CYSTITIS, PYELONEPHRITIS, AND CATHETER-ASSOCIATED UTI

The urinary tract has a portal to the outside, making it particularly susceptible to invasion by microbes. Bacteria normally inhabit the tissues around the urethral opening, and frequently colonize the urine. Among men, culture of a random initial void will find 1% to 5% colonized with *Escherichia coli*; urethral colonization is higher among men whose female sex partner has a UTI.⁴ Among women, urinary colonization rates are higher; the vaginal cavity and rectal opening are close to the urethral opening, and women have more moist periurethral areas where bacteria grow. On entering the urethra, the bacteria are more likely to ascend to the female bladder than the male bladder because of the shorter urethral length. The overall prevalence of asymptomatic bacteriuria (ASB) in women is 3.5%,⁵ but is much higher following sexual intercourse.⁶ Among both men and women, the prevalence of asymptomatic bacteriuria increases with age.^{5,7} Laboratory findings for ASB are the same as for other UTI syndromes (ie, a positive urine culture and urinalysis), but there are no signs or symptoms referable to the urinary tract (**Table 1**).

With the exception of during pregnancy, ASB is not a treatable condition. Treatment of ASB in the otherwise healthy individual often results in a symptomatic UTI,⁸ and increases selection for antibiotic-resistant bacteria. The Infectious Disease Society of America recommends against screening for and treating ASB among catheterized patients.⁹ However, physiologic changes during pregnancy make the

Table 1			
Urinary tract infection syndromes: laboratory findings, signs, and symptoms			
Syndrome	Laboratory Findings		Signs and Symptoms
	Culture	Urinalysis	
Asymptomatic bacteriuria (ASB)	+	+	None referable to urinary tract
Cystitis	+	+	Frequency, urgency, dysuria; less commonly suprapubic pressure, malaise, nocturia, incontinence (more common in children and elderly)
Pyelonephritis	+	+	Frequency, urgency, dysuria, back pain, flank pain, fever, chills, malaise, nausea, vomiting, anorexia, abdominal pain
Catheter-associated UTI	+	+	Fever, chills, altered mental state, malaise or lethargy with no other identified cause; flank pain, costovertebral angle tenderness, acute hematuria, pelvic discomfort If catheter has been removed: same as for cystitis or pyelonephritis

pregnant woman with ASB more susceptible to pyelonephritis.¹⁰ The prevalence of ASB in pregnancy ranges from 2% to 20%; and one-fifth to two-fifths of these may develop pyelonephritis if untreated.¹¹ Pyelonephritis can be life threatening to both the mother and infant.¹¹ Screening and treating ASB during pregnancy may reduce this risk by 77%.¹²

The high frequency of ASB does complicate the diagnosis of UTI, as urinary symptoms considered enigmatic of UTI, namely frequency, urgency and dysuria, are not solely caused by UTI. Vaginitis, chlamydia, and gonorrhea also cause urinary symptoms. Therefore, the chance of ASB and urinary symptoms occurring together by chance alone is not insignificant, especially as these conditions are also associated with sexual activity. By contrast, up to half of women at high risk of UTI (sexually active women aged 18–29 years) with frequency, urgency, and dysuria will have a negative urine culture when the limit of detection is 1000 cfu/mL urine.^{13,14}

In cystitis, urinary symptoms are confined to the bladder, although upper tract involvement occurs. Among premenopausal women, frequency, urgency, and dysuria are the most common symptoms. Among postmenopausal women, the elderly, and children, the patient may present with malaise, nocturia, incontinence, or a complaint of foul-smelling urine (see [Table 1](#)). Cystitis is very common. For example, among veteran users of the Veterans' Administration health care, the annual incidence was 4.3% among women and 1.7% among men.¹⁵ This figure is similar to population-based estimates from the Calgary Health Region of Canada, where the annual incidence of community-onset UTI identified using laboratory surveillance was 3% for females and 0.5% for males.¹⁶ Estimates based on self-reported history of physician diagnosis during the past year are higher: approximately 12.6% per year for women and 3.0% per year for men.¹⁷ Estimated lifetime risk of UTI for women based on self-reported history of physician diagnosis is 60.4%.¹⁸

Urinary symptoms may or may not be present in pyelonephritis; the patient may present with fever and chills, back pain, nausea, and vomiting (see [Table 1](#)). The incidence of pyelonephritis is an order of magnitude lower than cystitis (59.0/10,000 for females and 12.6/10,000 for males), but the patterns by age and sex are very similar.¹⁹ Risks are higher for females than for males, but these differences decrease with age ([Fig. 1](#)). In the United States, the incidence of hospitalization for acute pyelonephritis is 11.7 in 10,000 for women and 2.4 in 10,000 for men.²⁰ A population-based study in California estimated the incidence of hospitalization for pyelonephritis among children to be 31 in 100,000 in 2005. The incidence varied substantially by age, with children younger than 1 year having the highest rates.²¹

Every day that a urinary catheter is in place increases the risk of bacteriuria by 3% to 10%.²² However, unless there are symptoms referable to the urinary tract or there are generalized symptoms such as fever, chills, or malaise with no identifiable cause (see [Table 1](#)), catheter-associated bacteriuria is not a treatable condition.⁹ Catheters are the major risk factor for hospital-acquired UTI, which account for almost one-third of all hospital-acquired infections. The estimated rates of catheter-associated UTI vary by service: in an analysis of 15 hospitals in the Duke Infection Control Outreach Network, the rates were 1.83 per 1000 catheter days for patients in intensive care, compared with 1.55 per 1000 catheter days for other patients.²³ The risk of UTI with catheterization varies only slightly by catheter type. A multicenter, randomized controlled trial in the United Kingdom compared antimicrobial-impregnated, anti-septic-coated (silver alloy), and standard polytetrafluoroethylene-coated catheters in 7102 participants. Incidence of UTI any time up to 6 weeks following randomization in the 3 groups ranged from 10.6% to 12.6%, and was not significantly different between the groups.²⁴

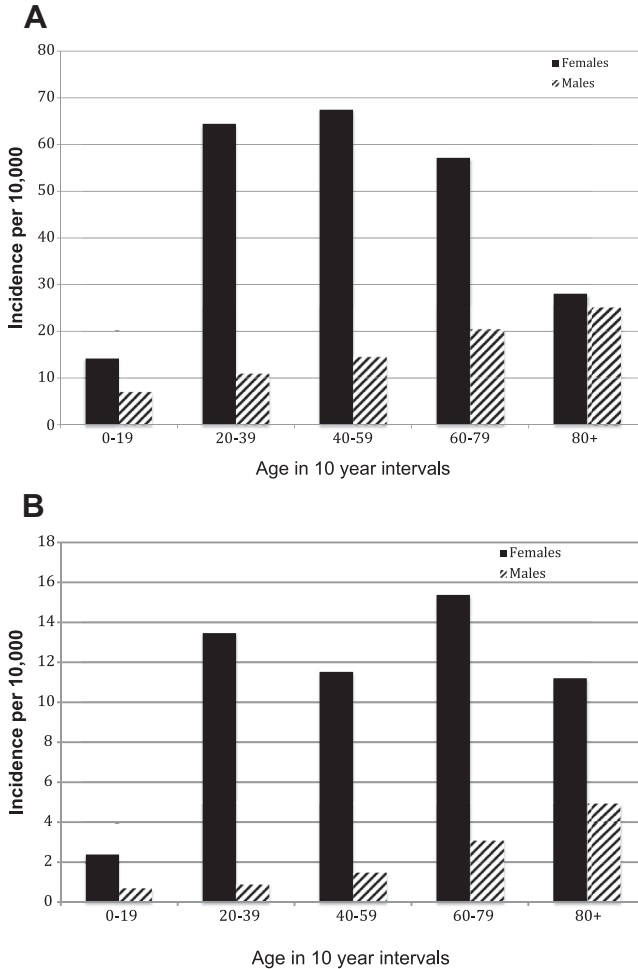


Fig. 1. Annual incidence of pyelonephritis per 10,000, by sex. (A) Pyelonephritis treated as outpatients. (B) Pyelonephritis treated in hospital. Data are taken from South Korean insurance claims, 1997 to 1999. (Adapted from Ki M, Park T, Choi B, et al. The epidemiology of acute pyelonephritis in South Korea, 1997–1999. *Am J Epidemiol* 2004;160:988; with permission.)

RECURRENCE

UTI has a propensity to recur with a frequency that varies by population (Table 2). Among children younger than 16 years with UTI participating in UTI intervention trials in Australia and Finland, the risk of recurrence within 1 year was 19% to 22%.^{25,26} The risk of recurrence is even higher among sexually active young women. In a Michigan study following 285 college women with first UTI for 6 months, the risk of a second was 24% within 6 months.²⁷ In a Seattle study of 796 women starting a new method of contraception, the risk of first UTI was 0.5 per person-year among college students and 0.3 per person-year among participants enrolled at a health maintenance organization.²⁸ Also in the Seattle study, women with a history of 2 or more UTIs compared

Table 2
Risk of recurrence by urinary syndrome and age group

Age Group	UTI	Pyelonephritis
Children	19%–22% within 5 y	21% within 5 y
Women	30%–50% per year	9% per year
Men	12% per year	6% per year

with those with only 1 or no UTI history had 2 to 5 times the risk of recurrence within a year.²⁸ A similar pattern is seen in postmenopausal women with a history of 3 or more UTIs in the previous year. In a Dutch double-blind noninferiority trial that included 252 postmenopausal women, 69.3% of those assigned to daily trimethoprim-sulfamethoxazole had recurrence of UTI within 12 months, compared with 79.1% assigned to lactobacilli prophylaxis. The mean number of recurrences in the 12-month follow-up period was 2.9 and 3.3, respectively.²⁹ UTI in men also has a tendency to recur. Among male veterans treated as outpatients for UTI at the Veteran Affairs system, the risk of recurrence within 30 days was 4.1%. Recurrence within 31 to 364 days occurred in 8.1%.³⁰

Pyelonephritis also recurs. In a Tennessee study, 21% of children with a first episode of pyelonephritis between the ages of 2 and 24 months had a second episode within 5 years.³¹ This finding was true even among children with normal ultrasonograms and voiding cystourethrograms: a New York retrospective telephone follow-up study of 119 children with a first UTI before 6 months of age with normal radiography found a recurrence rate of 20% by age 5 years.³² Among adults in South Korea, the 12-month risk of recurrence was 9.2% for females and 5.7% for males. However, risk of subsequent recurrences was substantially higher: 21.7% for a second recurrence to 53% for a fifth recurrence for females, and 21.6% for a second recurrence and 50% for a fifth recurrence for males.¹⁹

BACTERIOLOGY

Urine is a good medium for bacterial growth, so it is not surprising that many bacteria can grow in the urinary tract, and do so frequently (**Box 1, Fig. 2**). The bacteria colonizing the urinary tract do not cause disease in most cases because the host has many effective methods for rapidly removing bacteria from the system. These methods include urination and innate and adaptive host immune response. Bacteria that do cause UTI either have special features that enable them to survive in the urinary tract (eg, biofilm formation, urothelial cell invasion,³³ adhesins, toxins, and siderophores)³⁴ or inhabit a host that is compromised in a way that limits their ability to remove bacteria (eg, a catheter is in place). This fact explains the higher rate of UTI

Box 1 Bacteriology

- *Escherichia coli* causes the majority of asymptomatic bacteriuria, cystitis, pyelonephritis, and catheter-associated urinary tract infection (UTI)
- The proportion of UTI caused by species other than *Escherichia coli* is higher in recurring UTI and hospital-acquired UTI
- Antibiotic resistance is increasing, but patterns of resistance vary with patient population and geographic region

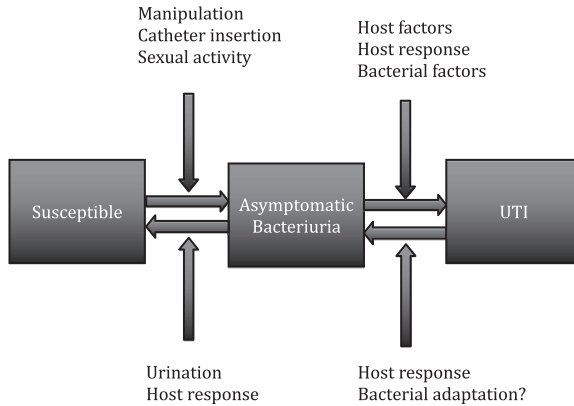


Fig. 2. Model of urinary tract infection syndromes.

among hospitalized patients: the prevalence of UTI on any 1 day among hospitalized patients is 1.1% to 6.5%; among those without urinary catheters or any exposure to urinary catheters, the point prevalence is 0.9%.³ By comparison, estimates for cystitis in the community are 0.5% to 3% per year for males and 3% to 12.6% per year for females.^{16,17}

E coli causes the majority of infections in all settings, for all syndromes and all age groups: 74.4% among outpatients regardless of age group, 65% of hospital-acquired infections, and 47% of health care-associated infections.¹⁶ The *E coli* that cause UTI are remarkably diverse, varying in the presence of known uropathogenic factors,^{35,36} and represent multiple different genetic lineages.^{37,38} Although the antibiotic resistances of uropathogenic *E coli* have increased over the past 30 years, resistance patterns are variable, depending on patient population and geographic region.³⁹

In addition to *E coli*, species that cause UTI, with varying frequency, are the gram-negative *Klebsiella* spp, *Pseudomonas aeruginosa*, and *Proteus* spp, and the gram-positive *Streptococcus agalactiae* and *Staphylococcus saprophyticus*. Individuals with recurrent UTI, males, those with a foreign body or obstruction, or with a urinary catheter, are more likely to have a UTI attributable to non-*E coli*.⁴⁰

RISK FACTORS

Risk factors for UTI (Box 2) can be divided into factors that expose the host to potential uropathogens, those that enhance colonization by the uropathogens, and those that lead the host to respond to colonization causing diseases (see Fig. 2). Uropathogens live in multiple environments, including the bowel, periurethral area, vaginal cavity, and urinary tract; they are transferred between individuals via person-to-person direct contact, including sexual activity, and via the fecal-oral route. Most uropathogens have special features that enable them to inhabit the urinary tract (see the section on bacteriology).

Bacteria found in the bowel, periurethral area, and vaginal cavity constantly move into the urinary tract. This movement is enhanced by manipulation, catheter insertion, and sexual activity. Females are particularly susceptible, because of the shorter distance between the urethral and anal opening and vaginal cavity, where potential uropathogens live. The distance from the urethral opening to the bladder is also shorter in

Box 2**Risk factors**

- Female sex
- Prior UTI
- Sexual activity
- Condom/diaphragm/spermicide use
- Vaginal infection
- Trauma/manipulation
- Diabetes
- Obesity
- Genetic susceptibility/anatomic abnormalities

females, making it easier for bacteria to ascend into the bladder, and females have more moist areas in the periurethrum where bacteria grow. However, symptoms only occur when the host response is engaged; the chances of immune-response engagement increase in those who are unable to urinate frequently, empty their bladder completely (such as those with neurogenic bladder or with obstruction), or are immunocompromised (those with comorbidities and increased age). ASB is generally transient, but some individuals are colonized for extended periods.⁴¹ Even when ASB is transient, uropathogens grow to substantial numbers (>100,000 cfu/mL urine), facilitating transmission to new hosts, some of whom may develop symptoms.

As noted earlier, UTI have a tendency to recur. A history of a previous UTI is a major risk factor for UTI. Whether this is a function of host behavior, host susceptibility, bacterial factors, or an interaction of the 3 is unclear. Host behavior is strongly associated with UTI. Sexual activity moves bacteria into the urethra in both males and females, increasing the risk for UTI. College women with their first UTI were 21 times more likely than controls to have engaged in vaginal intercourse 1 to 5 times during the previous 2 weeks.⁴² Condoms, diaphragms, and spermicide also are associated with an increase in UTI risk. Condom use may increase trauma; the increased risk associated with condom use is somewhat ameliorated by lubricant use.⁴³ A diaphragm may obstruct urine flow; there is also an independent effect of spermicide use on UTI risk, and spermicides are generally used with diaphragms.²⁷ Vaginal infections, such as bacterial vaginosis,^{44,45} can facilitate the growth of *E coli*, which probably accounts for their association with increased risk for UTI. Risk factors for pyelonephritis among otherwise healthy women are essentially the same as risk factors for cystitis.⁴⁶ Pregnant women are at higher risk of pyelonephritis, because of anatomic changes that occur during pregnancy.¹⁰

Placement of a catheter moves bacteria into the bladder, and creates an additional portal for bacterial invasion; catheter placement increases the risk of UTI by as much as 4-fold.³ However, any manipulation and presence of comorbidities increases UTI risk. In the United States, estimates of the point prevalence of UTI (based on the National Nursing Home Survey and National Home and Hospice Care Survey) are 5.2% among nursing home residents, 3.6% among those receiving home health care, and 3% of those receiving hospice care. UTI was the most common infection among those surveyed in all 3 sites.⁴⁷ Undergoing surgery for any reason greatly increases UTI risk, especially if it involves manipulation of the genitourinary tract and placement of a urinary catheter. Overall, UTI incidence in the 30 days following surgery is 1.7%, but is

2.6% among patients undergoing nonalimentary and noncolorectal tract surgery (95% confidence interval [CI] 2.2%–2.9%), compared with 5.6% (95% CI 4.6%–6.8%) for those undergoing abdominoperineal resection.⁴⁸ Risk of UTI following surgery for incontinence is substantially higher: in the 6 weeks following surgery, the incidence is reported to range from 10% to 32%.^{49,50}

The risk of UTI increases with age. The annual incidence of UTI among very old women in Sweden (85 years and older) was 29.6%. In this group, risk factors included vertebral fractures, incontinence, inflammatory rheumatic disease, and multi-infarct dementia.⁵¹ In the Leiden 85-Plus Study, the incidence of UTI among women was 12.8 per 100 person-years, and 7.8 per 100 person-years among men. The strongest predictors of UTI risk were severe cognitive impairment, disability in daily living, recent history of UTI, and urinary incontinence.⁵²

Type 2 diabetes also increases the risk of UTI. In a United Kingdom study conducted using the General Practice Research Database, younger men aged 18 to 39 years with diabetes were more than 4 times more likely to have UTI than their peers without diabetes.⁵³ The risk was also somewhat higher among individuals whose diabetes was poorly controlled. Overall, the adjusted relative risk of UTI among females with diabetes was 1.53 (95% CI 1.45–1.60), and 1.49 (95% CI 1.38–1.60) for males with diabetes (estimates adjusted for age and prior history of UTI). Obesity is a risk factor for diabetes, and also has been reported as a risk factor for UTI. A study conducted using insureds of the largest not-for-profit health care provider in Israel examined the joint association of obesity and diabetes on UTI risk. Unfortunately, this study did not take into account UTI history. After adjusting for age, body mass index (BMI), and vitamin D level, which is associated with increased risk of infection, diabetes increased the risk of UTI by 23% in males 24% in females. However, obesity was independently associated with UTI after adjustment for age, diabetes, and vitamin D levels: males with BMI of 50 kg/m² or higher were 2.38 (95% CI 1.40–4.03) times more likely than those with a BMI of less than 25 kg/m² to have a UTI; for females the increased risk was 1.25 (95% CI 1.03–1.52) (Fig. 3).⁵⁴ Because the United Kingdom and Israeli study were conducted using medical records, they were unable

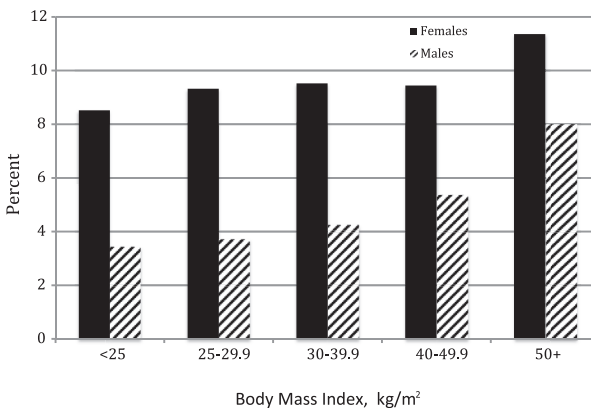


Fig. 3. Annual incidence of urinary tract infection per 100, by sex and body mass index. Individuals aged 18 years and older insured by the largest not-for-profit health care provider in Israel, 2009 to 2012. (Adapted from Saliba W, Barnett-Griness O, Rennert G. The association between obesity and urinary tract infection. *Eur J Intern Med* 2013;24:128; with permission.)

to adjust for sexual activity (see the article by Nicolle elsewhere in this issue for further discussion of diabetes and the risk of UTI).

Some individuals seem to be more inherently susceptible to UTI. Part of this susceptibility may be attributed to host behaviors such as frequency of sexual activity and urination habits. However, there is increasing evidence of genetic susceptibility. Women with recurrent cystitis and pyelonephritis are more likely than age-matched controls with no UTI history to report their female relatives as having a history of UTI.⁵⁵ This finding suggests that there might be a genetic component, but it is difficult with this study design to rule out the possibility that women with recurring UTI might be more likely to know their family history. Stronger evidence derives from studies demonstrating polymorphisms in genes coding for inflammatory response (toll-like receptors, interferon regulatory factors, and chemokine receptors) between individuals with ASB and pyelonephritis.^{56,57} However, it is most likely that variation in disease severity results from an interaction between bacterial virulence genes and host response.⁵⁸

DISEASE BURDEN

The vast majority of UTIs are confined to the bladder (**Box 3**). Typical symptoms are hematuria, dysuria, urgency, frequency, nocturia, offensive smell, and abdominal pain. In a study of 684 women aged 18 to 70 years with UTI, participants reported an average of 3.83 symptom days, 2.89 restricted-activity days, and 3.13 days during which they were unwell. Most symptoms lasted no more than 3 days, with hematuria having the shortest duration (1.88 days) and urinary frequency the longest (3.14 days).⁵⁹ The risk that cystitis will progress to pyelonephritis is low, less than 1% (reviewed in Ref.⁶⁰), although a recent UTI does increase the risk of pyelonephritis by 4.4 times (95% CI 2.8–7.10); note that women with pyelonephritis were 5.6 times more likely than controls to engage in sexual intercourse 3 or more times per week. The estimated annual direct and indirect cost of UTI in the United States is \$2.3 billion in 2010 dollars.⁶⁰

Acute pyelonephritis among adults results in hospitalization for 10% to 30% of patients. The direct and indirect costs were estimated as \$2.14 billion in 2000 (which is ~\$2.9 billion in 2013).²⁰ Patients with acute pyelonephritis are increasingly managed as outpatients, greatly reducing costs.⁶¹ However, with increasing antibiotic resistance, the need for intravenous administration of antibiotics—and hospital admission—may increase. Pyelonephritis in pregnancy can cause serious morbidity. In a study conducted using a Nationwide Inpatient Sample in 2006, pregnant patients hospitalized for pyelonephritis stayed a mean of 2.8 days, for an estimated annual cost of \$263 million in 2012 dollars. Although the risk of death was very low, almost 2% had sepsis, 0.77% had acute respiratory failure, and 3.77% had threatened preterm labor.⁶²

The urinary tract is a frequent source of bacteremia, and the urinary tract is the most common source of *E coli* bacteremia. In Olmstead County the age-adjusted incidence of gram-negative bacteremic UTI was 55.3 per 100,000 for females and 44.6 per

Box 3

Disease burden

- Women with UTI average 3.83 symptom days and 2.89 restricted-activity days
- Risk of cystitis progressing to pyelonephritis is less than 1%
- Urinary tract is the most common source of *E coli* bacteremia

100,000 for males. Risk of bacteremia increased sharply at ages 60 to 79, and exceeded 4 per 1000 among those 80 and older, among whom the risks were higher in males than in females. The mortality rate after 28 days for any cause was 4.9%.⁶³ Risk factors for bacteremia among inpatients identified in a Missouri study of 156 patients with *E coli* bacteriuria at the time of admission included benign prostatic hyperplasia, a history of urogenital surgery, pyelonephritis, and presentation with hesitancy/retention or fever.⁶⁴

The risk of bacteremia and subsequent mortality is substantially higher among inpatients with urinary catheters. In a United Kingdom study of 559 bacteremic episodes among 437 patients, almost 15% were associated with urinary catheters, second only to bacteremia associated with central venous catheters.⁶⁵ Among those with catheter-associated bacteremic UTI, the risk of mortality within 7 days was 30.1%.⁶⁵

SUMMARY

- The bladder is continuously invaded by bacteria, which can grow to substantial numbers before spontaneous clearance.
- Host factors, host behaviors, and bacterial characteristics are risk factors for the development of symptoms.
- UTI occurs more often in females than in males.
- Except during pregnancy, ASB is not a treatable condition.
- Cystitis and pyelonephritis are likely to recur, regardless of age, gender, or treatment.
- The gram-negative rod *E coli* is the most common cause of UTI in all settings, and is transmitted by person-to-person direct contact and the fecal-oral route.
- The proportion of UTI caused by species other than *E coli* is higher in recurring UTI and hospital-acquired UTI.
- The urinary tract is the most common source of bacteremia attributable to *E coli*.

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