Cystitis and Pyelonephritis
Diagnosis, Treatment, and Prevention

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KEYWORDS

- Urinary tract infection
- Recurrent UTI
- Pyelonephritis
- Cystitis
- Prevention
- Treatment

KEY POINTS

- Uncomplicated urinary tract infections occur in otherwise healthy, nonpregnant women with normal genitourinary tracts and no recent history of instrumentation, including bladder catheterization.
- The combination of dysuria and frequency in the absence of vaginal discharge and vaginal irritation is more than 90% predictive for cystitis. Symptoms are less reliable in postmenopausal women owing to the high prevalence of chronic urinary complaints.
- Routine use of imaging is not necessary for the diagnosis of uncomplicated cystitis or pyelonephritis.
- The initial antibiotic choice should be based on individual patient factors and local antibiotic resistance patterns. Duration of treatment ranges from 3 to 5 days for uncomplicated cystitis to 7 to 14 days for pyelonephritis.
- There is a need for additional data to support the use of nonantimicrobial prophylaxis for recurrent urinary tract infections.

INTRODUCTION

Urinary tract infections (UTIs) are the most common bacterial infection primary care clinicians will encounter in office practice, accounting for approximately 5 million primary care office visits in 2007.1 UTIs are much more common in women than in men. During their lifetime, 40% to 50% of women are diagnosed and treated for a UTI, with most being diagnosed before the age of 25.2

As health care costs continue to rise and antimicrobial resistance becomes more widespread, clinicians must constantly review and adjust their practice patterns to provide the best, most effective care to their patients and the population as a whole. This review focuses on the diagnosis, treatment, and prevention of the most common UTIs, namely, cystitis and pyelonephritis.

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DEFINITIONS

UTI is a general term used to designate any infection of the urinary tract and includes asymptomatic bacteriuria, cystitis, and pyelonephritis. Asymptomatic bacteriuria by definition occurs in patients without urinary symptoms who have growth of $10^5$ bacteria or more in 2 consecutive urine specimens in women or a single sample in men.3,4

Cystitis and pyelonephritis are symptomatic UTIs involving the bladder and kidneys, respectively, and are further classified as uncomplicated or complicated based on risk factors in the affected patient5 (Fig. 1). This classification is aimed to help identify those patients who may need additional diagnostic tests, broader spectrum antibiotics, and/or longer durations of treatment.

An uncomplicated UTI is one that occurs in an otherwise healthy, nonpregnant woman with a normal genitourinary tract and no recent history of instrumentation, including bladder catheterization.4,6 All other UTIs are classified as complicated. Note that, in this classification system, women with diabetes are automatically classified as having complicated infections. However, many experts would consider women with well-controlled diabetes who otherwise meet the criteria for an uncomplicated infection to have an uncomplicated UTI.6

Both cystitis and pyelonephritis may occur as uncomplicated and complicated infections, depending on patient risk factors. Although cystitis can progress to acute pyelonephritis, this occurrence is rare.7 More commonly, acute pyelonephritis is thought to develop as a primary infection with both patient and bacterial factors playing a role in its occurrence.8 Complications associated with pyelonephritis include sepsis, acute kidney injury, development of renal or perinephric abscess, and emphysematous pyelonephritis.9

Recurrent UTIs are commonly defined as 3 or more infections within a 12-month period or 2 or more infections within a 6-month period.4,10,11 Of women who have a UTI, 20% to 30% will have a recurrence within 3 months.10,12

RISK FACTORS

Premenopausal Women

In young, healthy, premenopausal women, the most common identifiable risk factors for UTI are recent sexual intercourse, spermicide use, and a previous history of UTI.13

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Fig. 1. Classification of UTIs.
These risk factors also have been identified in women with recurrent cystitis and pyelonephritis. Another significant risk factor for recurrent cystitis and pyelonephritis include a mother with history of UTIs. Additionally, pyelonephritis is associated with incontinence in women less than 30 years of age and individuals with diabetes (Table 1).

There is no consistent evidence to show that behaviors such as postcoital voiding, hydration status, wiping patterns, tampon use, douching, type of underwear, or use of hot tubs are significantly associated with a risk for recurrent UTIs.

**Postmenopausal Women**

Postmenopausal women are at increased risk of UTI for a number of reasons, including the lower levels of vaginal and systemic estrogen, which is thought to play a role in continence, vaginal pH, and maintaining the normal vaginal flora. Other risk factors for recurrent UTI in postmenopausal women include a history of UTI before menopause, urinary incontinence, cystocele, vaginal prolapse, incomplete bladder emptying, and a change in the vaginal flora.

**PRESENTATION AND DIAGNOSIS**

The clinical presentation of acute cystitis can include dysuria, frequency, urgency, suprapubic pain, and hematuria. Women presenting with a constellation of symptoms consistent with cystitis are more likely to have a culture-proven infection than women presenting with just 1 symptom.

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**Table 1**

**Summary of risk factors and diagnosis for common UTIs**

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Risk Factors</th>
<th>Urine Culture Needed for Diagnosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncomplicated cystitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal women</td>
<td>Recent sexual intercourse, Spermicide use, Previous history of UTI</td>
<td>No</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>History of UTI, Urinary incontinence, Cystocele, Vaginal prolapse, Incomplete bladder emptying</td>
<td>Should be considered if ≤1 symptom present</td>
</tr>
<tr>
<td><strong>Pyelonephritis</strong></td>
<td>Recent sexual intercourse, Spermicide use, Previous history of UTI, Mother with UTIs, Incontinence women &gt;30 years, Diabetes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Recurrent UTI</strong></td>
<td>Recent sexual intercourse, Spermicide use, Previous history of UTI, Mother with UTIs</td>
<td>Yes, at least once while symptoms are present</td>
</tr>
</tbody>
</table>

Data from Refs.12–21
The presence of fever, chills, flank pain, nausea, vomiting, and/or costovertebral angle tenderness suggest a diagnosis of pyelonephritis. Pyelonephritis may occur in patients with or without typical urinary symptoms.

Urine culture is the gold standard diagnostic test for all UTIs. However, it may be unnecessary for diagnosis in many situations. The diagnostic workup depends on the type of infection, patient factors, and whether the infection is complicated (see Table 1).

**Uncomplicated Cystitis**

**Premenopausal women**
Symptomatology alone has a high predictive value of acute cystitis in premenopausal women. Among women who have had at least 1 UTI, self-diagnosis of symptoms correlates with culture-proven UTI greater than 80% of the time. The combination of dysuria and frequency in the absence of vaginal discharge and vaginal irritation has a predictive value for cystitis of more than 90%. In these situations, it is recommended that the diagnosis be made without any confirmatory laboratory testing. Urine dipstick testing should be performed when only 1 symptom is present or if nonspecific symptoms are present. A positive urine dipstick test for nitrites or leukocyte esterase gives an 80% probability of UTI. A urine culture should be obtained if the urine dipstick testing is negative, or if symptoms fail to resolve or recur within 4 weeks of completing treatment.

**Postmenopausal women**
Older women with acute cystitis may present a diagnostic challenge because the prevalence of chronic urinary frequency, urgency, and incontinence is higher in this population. Therefore, when considering a UTI in older women, it is important to evaluate urinary symptoms in relation to an individual’s baseline.

Asymptomatic bacteriuria becomes more common with age, with a prevalence of 30% to 50% in women greater than 70 years of age, which makes routine urine testing less helpful. Urine dipstick testing, urinalysis, and urine culture should not be routinely obtained in women aged 65 years or older because there is a high false-positive rate in this population. Instead, in older women with a low pretest probability of UTI, urine dipstick testing can be used to rule out an infection.

A diagnosis of a UTI in postmenopausal women should be made with a urine culture. Urine culture should be obtained when there are at least 2 new or worsening urinary symptoms, fever, or dysuria present for less than 1 week. In patients with baseline cognitive impairment, an acute and persistent change in mental status that does not respond to the usual interventions should also prompt obtaining a urine culture.

**Recurrent Cystitis**
The Canadian Urologic Association and European Urologic Association recommend that a diagnosis of recurrent UTI be confirmed with urine culture, at least once while symptoms are present. A negative urine culture should prompt an investigation into other causes for the symptoms the patient is experiencing. Further investigations, such as cystoscopy or radiographic imaging with computed tomography scan of the abdomen and pelvis, should be reserved for women with risk factors for an obstruction or a structural abnormality. The American College of Radiology Appropriateness Criteria can guide the choice of additional imaging based on the suspected abnormality (Table 2).
Uncomplicated Pyelonephritis

Urinalysis for white blood cells, red blood cells, and nitrites is recommended when a diagnosis of pyelonephritis is suspected, because the results of this test are available faster than a urine culture. A urine culture and sensitivity testing are recommended for all cases of pyelonephritis. The American College of Radiology does not recommend routine use of imaging in cases of suspected acute, uncomplicated pyelonephritis. Imaging is reserved for patients who have, or are suspected of having, complicated pyelonephritis: patients with structural abnormalities, a history of recent instrumentation, indwelling urinary catheters, immunocompromised patients, and pyelonephritis in men. Imaging may also be considered for patients who do not respond to appropriate antibiotic therapy within 72 hours of initiation. In these cases, a computed tomography scan of the abdomen/pelvis with intravenous (IV) contrast is recommended.

Complicated Cystitis and Pyelonephritis

A urine culture should be performed for all suspected cases of complicated cystitis and pyelonephritis. A computed tomography scan of the abdomen/pelvis with IV contrast is recommended over MRI and ultrasound examination as the imaging test of choice for complicated pyelonephritis because it is the most sensitive method for detecting urolithiasis, perinephric abscess, and emphysematous pyelonephritis. Ultrasound examinations and MRI can be used in patients with contrast allergy, but they are less sensitive for small calculi and for emphysematous pyelonephritis.

CLINICAL MANAGEMENT AND TREATMENT

Escherichia coli is implicated in 75% to 95% of acute uncomplicated cystitis (AUC) and pyelonephritis. Other bacteria frequently implicated in UTIs are Proteus mirabilis, Klebsiella pneumonia, and S saprophyticus. Antibiotics are the mainstay of treatment for UTIs. The choice of antibiotic depends on the type of infection, complications, and local antimicrobial resistance patterns. The increasing antimicrobial resistance of E coli and the other urinary pathogens has influenced the formation of guidelines for UTI treatment and led to the study of alternative methods of treatment for UTI.
It has been shown that 25% to 50% of women with urinary symptoms consistent with AUC recover within 1 week without antibiotics. In an effort to decrease the number of antibiotic prescriptions for UTIs, a number of studies have looked at using nonsteroidal antiinflammatory drugs as a symptomatic treatment in place of antibiotics for treatment of AUC. However, these studies have shown that nonsteroidal antiinflammatory drugs are inferior to antibiotics and, therefore, nonsteroidal antiinflammatory drugs are not recommended as a method of treatment for AUC.

**Acute Uncomplicated Cystitis**

There are several approaches to initiating antibiotics in women with AUC, including telephone management, patient-initiated treatment, and traditional office-visit based treatment. Telephone-based algorithms for the management of AUC have proven to be safe and cost effective, with an increase in patient satisfaction and without an increased risk of complications. Using a telephone-based algorithm, appropriate antibiotics can be prescribed without an office visit, once risk factors for complicated infection are ruled out, and it is established that there is a high probability of infection.

Women with recurrent AUC may be managed with patient-initiated treatment. In this method, a patient is given a prescription for an antibiotic, which can be filled when she experiences the symptoms of a UTI. If symptoms do not resolve after treatment is completed, the patient is instructed to come in for an office visit. The major risk of this method is that sexually transmitted infections such as chlamydia may be mistaken for an AUC by the patient and thus go unrecognized and untreated. Therefore, it is recommended that patient-initiated treatment not be used in women at high risk for sexually transmitted infections.

When seeing a patient in the office for a suspected AUC, a delayed antibiotic approach may be used. In this method, patients are given a prescription for antibiotics, but are asked not to fill it unless they feel that they need it (eg, in cases of worsening or persistent symptoms). In a study evaluating this approach, 37% of women agreed to delay antibiotic treatment and 55% of those women improved without using antibiotics. There were no complications from delaying treatment noted in this study.

**Choice and duration of antibiotic**

The initial antibiotic choice should be based on individual patient factors and local antibiotic resistance patterns. The current Infectious Diseases Society of America (IDSA) guidelines recommend nitrofurantoin for 5 days or trimethoprim-sulfamethoxazole (TMP-SMX) for 3 days as a first-line treatment for an AUC (Table 3). TMP-SMX should not be used empirically in areas where known antimicrobial resistance rates are 20% or greater. A single dose of fosfomycin is also appropriate for the empiric treatment of AUC, but it may have a lower efficacy when compared with other acceptable treatments. A 3-day course of a fluoroquinolone can be used for AUC, but to prevent the development of antimicrobial resistance, it is recommended that fluoroquinolones be reserved for more severe infections.

Do not use amoxicillin or ampicillin empirically owing to high resistance rates. Cephalosporins and amoxicillin-clavulanate are less efficacious and should be not be used as empiric treatment, but can be used in 3- to 7-day regimens if other antibiotics cannot be used.

**Pyelonephritis**

As with an AUC, the initial antibiotic choice for pyelonephritis should be based on individual patient factors and local antibiotic resistance patterns. Once the bacterial pathogen has been identified, the antibiotic regimen should be tailored appropriately.
For outpatient treatment, the current IDSA guidelines recommend the use of an oral fluoroquinolone (ciprofloxacin or levofloxacin) as the preferred empiric therapy when local fluoroquinolone resistance rates are known to be less than 10%. If local resistance rates are 10% or greater, a one-time IV dose of ceftriaxone or another long-acting antibiotic should be given with an oral fluoroquinolone. TMP-SMX may also be used as empiric therapy with a one-time IV dose of ceftriaxone if susceptibilities are not known. Oral cephalosporins have lower efficacy compared with other agents and should only be used for the treatment of pyelonephritis if susceptibilities are known and there is no other appropriate choice. Ampicillin should only be used if infection with an Enterococcus is suspected owing to high resistance rates for the typical gram-negative urinary pathogens.6

For inpatient treatment, the IDSA recommends initiating treatment with an IV antibiotic that is appropriate based on local resistance patterns and patient factors. Fluoroquinolones, extended-spectrum penicillins, extended-spectrum cephalosporins, carbapenems, and aminoglycosides are all appropriate choices for empiric therapy.6 The IDSA does not provide specific guidelines for when to transition to oral therapy owing to a lack of available evidence on this topic. One common practice is to choose an appropriate oral regimen once susceptibilities are available. The duration of treatment varies based on the specific medication used (Table 4). With increasing antimicrobial resistance, effort should be made to use the shortest duration of antibiotics that is appropriate.32 Fluoroquinolones have the shortest recommended length of treatment of 5 to 7 days depending on the specific drug used. The IDSA recommends that TMP-SMX be used for a total of 14 days and that beta-lactams be used for 10 to 14 days for pyelonephritis.6 However, a metaanalysis

### Table 3

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose (Oral)</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin monohydrate</td>
<td>100 mg BID (\times 5) d</td>
<td>—</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>160/800 mg (double strength) BID (\times 3) d</td>
<td>Not for use when resistance rates are (\geq 20)%</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3g once</td>
<td>—</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>400 mg BID (\times 3)–7 d</td>
<td>Not available in North America</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin 250 mg BID (\times 3) d, Ofloxacin 200 mg BID (\times 3) d, Levofloxacin 250 mg daily (\times 3) d</td>
<td>Not recommended as a first-line agent; use only if no other agent is appropriate</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>500/125 mg BID (\times 3) d</td>
<td>Avoid unless no other agent is appropriate</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cefdinir 100 mg BID (\times 5) d, Cefaclor 250 mg TID (\times 5) d, Cefpodoxime-proxetil 100 mg BID (\times 3) d</td>
<td>Avoid unless no other agent is appropriate</td>
</tr>
</tbody>
</table>

**Abbreviations:** BID, 2 times per day; TID, 3 times per day.

comparing the duration of treatment for pyelonephritis found that a treatment duration of 7 days or less was equivalent to a longer treatment duration and did not differ based on the type of antibiotic used. Subsequently, another study comparing 7 days of TMP-SMX with 7 days of ciprofloxacin showed that the regimens were equally effective. The duration of treatment does not need to be extended for patients with positive blood cultures.

PREVENTION OF RECURRENT URINARY TRACT INFECTIONS

Both nonantimicrobial and antimicrobial prophylaxis regimens have been studied in women with recurrent UTIs (Table 5). With the exception of vaginal estrogen, the data supporting nonantimicrobial regimens is not robust, and additional studies are needed before routinely recommending these methods.

Vaginal Estrogen

Estrogen has a role in maintaining vaginal pH, normal vaginal flora, and urinary continence. Lower levels of estrogen in postmenopausal women are thought to be an important contributor to the higher incidence of UTIs in this population. A Cochrane review found that vaginal estrogen, used as either a cream or a ring/pessary, significantly decreased the number of UTIs in postmenopausal women. Oral estrogen was not shown to decrease recurrent UTIs in postmenopausal women.

Probiotics

Probiotics are thought to prevent UTIs by helping to restore the normal vaginal microbiome. A Cochrane review of 9 studies investigating the use of *Lactobacillus* spp. for the prevention of recurrent, symptomatic UTIs in women found no decrease in the risk of recurrent UTI. Additional studies are needed before routinely recommending the use of probiotics to prevent recurrent UTIs.

Cranberries

The exact mechanism by which cranberries prevent UTIs is unknown. It is thought that the proanthocyanidins found in cranberries and cranberry products inhibit *E coli* from adhering to the bladder walls. The amount of cranberry juice recommended to prevent...
UTI is 300 mL daily, an amount that many women find difficult to ingest. Capsules and tablets are better tolerated. However, the processing of cranberries may affect the amount of proanthocyanidins in cranberry tablets and capsules. A Cochrane review of 24 studies did not show any decrease in the risk of recurrent UTI in women using a variety of cranberry products. Further studies are needed before routinely recommending cranberry products to prevent UTI.

**D-Mannose**

One of the mechanisms by which *E coli* causes cystitis is by adhering to various proteins that line the bladder wall. D-Mannose is thought to interfere with the ability of *E coli* to bind to the urothelium. Two small studies have shown that D-mannose may be effective in preventing recurrent UTIs in women. However, additional studies are needed before routinely recommending this method as a reliable preventive measure.

**Hyaluronic Acid and Chondroitin Sulfate**

The glycosaminoglycan layer lining the bladder wall, composed of hyaluronic acid and chondroitin sulfate, is thought to play a role in preventing the adherence of bacteria to the urothelium. A damaged glycosaminoglycan layer could, therefore, theoretically lead to an increased risk of recurrent UTIs. Two small, randomized, controlled trials have shown that instillation of a solution of hyaluronic acid and chondroitin sulfate can prevent recurrent UTIs. Additional studies are needed before recommending this method as a routine preventive measure.

**Antibiotics**

Antibiotic prophylaxis should be reserved for those women in whom nonantimicrobial interventions have failed. Various low-dose, once daily, or postcoital antibiotic

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**Table 5**

**Prophylaxis for recurrent UTI**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal estrogen</td>
<td>Estradiol ring 2 mg&lt;br&gt;Estradiol cream 0.5 mg nightly x 2 wk; then twice weekly</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Studied regimens include:&lt;br&gt;Vaginal suppositories 2×/week to monthly&lt;br&gt;Oral capsule daily to BID&lt;br&gt;Oral drink 5 d/mo</td>
</tr>
<tr>
<td>Cranberries</td>
<td>300 mL juice = 36 mg proanthocyanidins</td>
</tr>
<tr>
<td>D-Mannose</td>
<td>2 g daily</td>
</tr>
<tr>
<td>Hyaluronic acid and Chondroitin sulfate</td>
<td>800 mg and 1 g in 50-mL solution via instillation into bladder</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Regimens vary&lt;br&gt;May dose daily or postcoital&lt;br&gt;Nitrofurantoin 50–100 mg daily&lt;br&gt;TMP-SMX 40/200 daily = ½ single strength&lt;br&gt;Cephalexin 125 mg daily&lt;br&gt;Norfloxacin 200 mg daily</td>
</tr>
</tbody>
</table>

**Abbreviation:** BID, 2 times per day.

* Data are not sufficient to routinely recommend as prophylaxis.
* Processing of cranberries into capsules and tablets may affect the amount of proanthocyanidins they contain.

Data from Refs. 4,10,12,35–40
regimens have been shown to be effective (see Table 5). A Cochrane review of antibiotic regimens for prevention of UTI showed that all studied regimens are effective in preventing UTI, and there was not enough information to conclude that one regimen was superior to another. Shortly after antibiotics are discontinued, the frequency of UTIs returned to baseline level.

SUMMARY

Cystitis and pyelonephritis are the most common UTIs. The classification of UTIs as complicated or uncomplicated is based on patient factors, with uncomplicated infections defined as those occurring in an otherwise healthy, nonpregnant woman with a normal genitourinary tract and no recent history of instrumentation. *Escherichia coli*, *P mirabilis*, *Klebsiella pneumoniae*, and *S saprophyticus* are the major pathogens that cause UTIs. The diagnosis and treatment of UTIs requires attention to the growing resistance of these pathogens to antibiotics. Knowledge of local antimicrobial resistance patterns is necessary when choosing an antibiotic. The most appropriate, narrowest-spectrum antibiotic should be prescribed for the shortest duration to prevent the further development of antimicrobial resistance.

REFERENCES


33. Fox MT, Melia MT, Same RG, et al. A seven-day course of TMP-SMX may be as effective as a seven-day course of ciprofloxacin for the treatment of pyelonephritis. Am J Med 2017;130:842–5.


