UpToDate® Official reprint from UpToDate®
www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

Acute simple cystitis in females

Author: Kalpana Gupta, MD, MPH
Section Editor: Stephen B Calderwood, MD
Deputy Editor: Allyson Bloom, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Dec 2022. | **This topic last updated:** Nov 21, 2022.

INTRODUCTION

Urinary tract infections (UTIs) include cystitis (infection of the bladder/lower urinary tract) and pyelonephritis (infection of the kidney/upper urinary tract). In females, the pathogenesis of UTIs begins with colonization of the vaginal introitus by uropathogens from the fecal flora, followed by ascension via the urethra into the bladder and, in the case of pyelonephritis, to the kidneys via the ureters.

This topic will review the approach to females with typical symptoms of cystitis when there is no concern that the infection has extended beyond the bladder. We consider this to be acute simple cystitis.
(Related Pathway(s): Urinary tract infection (UTI): Empiric antibiotic selection for acute simple cystitis in female adults.)

When there is concern that the infection has possibly extended beyond the bladder (eg, when there is flank pain or other features suggestive of pyelonephritis, fever, and/or other signs of systemic illness, including sepsis) we consider this to be a complicated UTI. This approach to categorizing UTI (table 1) differs from other conventions, as discussed in detail below.

Our approach to the diagnosis and management of complicated UTI is discussed elsewhere. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults".)
(Related Pathway(s): Urinary tract infection (UTI): Empiric antibiotic selection for acute complicated UTI in adults.)

Additionally, acute simple cystitis in men and UTIs in special populations are discussed elsewhere:

- (See "Acute simple cystitis in adult males".)
- (See "Urinary tract infections and asymptomatic bacteriuria in pregnancy".)
- (See "Catheter-associated urinary tract infection in adults".)
- (See "Urinary tract infection in kidney transplant recipients".)
- (See "Recurrent simple cystitis in women".)

Asymptomatic bacteriuria is also discussed in detail elsewhere. (See "Asymptomatic bacteriuria in adults".)

Urinary tract infection in children is also discussed separately. (See "Urinary tract infections in children: Epidemiology and risk factors" and "Urinary tract infections in children: Long-term management and prevention" and "Urinary tract infections in infants and children older than one month: Clinical features and diagnosis" and "Urinary tract infections in infants older than one month and young children: Acute management, imaging, and prognosis".)

TERMINOLOGY

We use the term acute simple cystitis to refer to an acute urinary tract infection (UTI) that is presumed to be confined to the bladder (table 1). Such infections **lack** signs or symptoms that suggest an infection extending beyond the bladder, which include:

- Fever (>99.9°F/37.7°C) – This temperature threshold is not well defined and should be individualized, taking into account baseline temperature, other potential contributors to an elevated temperature, and the risk of poor outcomes should empiric antimicrobial therapy be inappropriate.
- Other signs or symptoms of systemic illness (including chills or rigors, significant fatigue or malaise beyond baseline).
- Flank pain.
- Costovertebral angle tenderness.

If any of these signs or symptoms are present in the setting of pyuria and bacteriuria, we consider the patient to have acute complicated UTI and manage the patient differently. By this definition, pyelonephritis is a complicated UTI, regardless of patient characteristics. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults".)

We do not automatically consider patients with underlying urologic abnormalities (such as nephrolithiasis, strictures, stents, or urinary diversions), immunocompromising conditions (such as neutropenia or advanced HIV infection), or poorly controlled diabetes mellitus to have a complicated UTI if they have no concerning symptoms for upper tract or systemic infection. However, such patients can be at higher risk for more serious infection and have

not traditionally been included in studies evaluating the antibiotic regimens we typically use for acute simple cystitis. Thus, we follow such patients more closely and/or have a low threshold to manage them as complicated UTI (eg, if they have subtle signs or symptoms that could be suggestive of more extensive infection). Many patients with significant urologic abnormalities come to clinical attention for UTI because of signs or symptoms consistent with complicated UTI as defined here (rather than features of simple cystitis alone).

Certain populations, such as pregnant individuals and renal transplant recipients, have unique management considerations and thus are not included in the above categorization. These populations are discussed elsewhere. (See "Urinary tract infections and asymptomatic bacteriuria in pregnancy" and "Urinary tract infection in kidney transplant recipients".)

These definitions of acute simple cystitis and complicated UTI are different from other categorizations, which themselves are somewhat variable. Specifically, cystitis or pyelonephritis in a nonpregnant premenopausal woman without underlying urologic abnormalities has traditionally been termed acute uncomplicated UTI [1], and complicated UTI has been defined, for the purposes of treatment trials, as cystitis or pyelonephritis in a patient with underlying urologic abnormalities. Individuals who do not fit into either category have often been treated as having a complicated UTI by default. Rather than use this convention, we favor an approach to treatment based on the presumed extent of infection and severity of illness. Since complicated UTI, as defined here, is a more serious infection than simple cystitis, the efficacy of an antimicrobial agent is of greater importance, and certain agents used for simple cystitis should not be used for complicated UTI because they do not achieve adequate levels in tissue, which may be important for cure. Risk for infection with drug-resistant organisms is a consideration in antibiotic selection for both simple cystitis and acute complicated UTI.

Females categorized as having acute uncomplicated cystitis according to the traditional definition would fall under the definition of acute simple cystitis that we use here.

EPIDEMIOLOGY

Cystitis among females is extremely common [2,3]. The shorter distance from the anus to the urethra likely explains why females are at higher risk for urinary tract infections (UTIs) than men.

Among otherwise healthy females, risk factors for cystitis include recent sexual intercourse and a history of UTI [4,5]. Use of spermicide-coated condoms, diaphragms, and spermicides alone are also associated with an increased cystitis risk.

Other comorbidities, such as diabetes mellitus and structural or functional urinary tract abnormalities, can also increase the risk of cystitis [2]. Although patients with these comorbidities have traditionally been categorized as having complicated UTI, our approach does not necessarily categorize them as such.

MICROBIOLOGY

Microbial spectrum — *Escherichia coli* is the most frequent microbial cause of simple cystitis (75 to 95 percent of cases), with occasional infections caused by other species of Enterobacteriaceae (such as *Klebsiella pneumoniae* and *Proteus mirabilis*) and other bacteria, such as *Staphylococcus saprophyticus* [6,7]. Other gram-negative and gram-positive species are infrequently isolated in acute simple cystitis in the absence of antimicrobial or health care exposures.

The microbial spectrum of simple cystitis in patients with recent antimicrobial or other health care exposures may be broader and also includes other gram-negative bacilli (eg, *Pseudomonas*), enterococci, and staphylococci. Thus, culture and susceptibility testing are essential for management in patients who have such risk factors (table 2). Even in the absence of specific risk factors, resistance in *E. coli* can be a major issue.

Among otherwise healthy nonpregnant females, the isolation of organisms such as lactobacilli, enterococci, Group B streptococci, and coagulase-negative staphylococci other than *S. saprophyticus* from voided midstream urine most commonly represents contamination of the urine specimen [8,9]. Nevertheless, it may be appropriate to consider these organisms the likely causative agent in symptomatic females when found in voided midstream urine at high counts and with pure growth (ie, without growth of other bacteria). That such organisms are rarely the cause of acute simple cystitis in such females is supported by a study of 202 premenopausal, nonpregnant females with acute cystitis who collected a midstream, clean-catch urine, and subsequently underwent urethral catheterization to collect a bladder urine specimen [10]. There was high concordance between growth on voided and catheterized specimens for *E. coli* (even at counts as low as 10 colony-forming units [CFU]/mL), *K. pneumoniae*, and *S. saprophyticus*. In contrast, enterococci and Group B streptococci were isolated from 20 and 25 voided specimens, respectively, but only from two corresponding catheterized specimens each. In the majority of specimens with these organisms, growth was $<10^4$ CFU/mL, and *E. coli* was also isolated.

Resistance trends in E. coli — Expected susceptibility patterns of *E. coli* should inform the empiric antimicrobial selection for cystitis. Increasing rates of resistance have been reported globally. Risk factors for urinary tract infection (UTI) with resistant organisms include recent broad-spectrum antimicrobial use, health care exposures, and travel to parts of the world where multidrug-resistant organisms are prevalent [11-15] (table 2). Ongoing monitoring

of local prevalence of resistance is necessary for optimization of empiric therapy. (See 'Empiric antimicrobial selection' below.)

The in vitro susceptibility of *E. coli* varies considerably by geographic region. In four large studies, overall resistance rates were higher in medical centers in the United States than in Canada, and higher in Portugal and Spain than in other European countries [16-19]. In general, resistance rates >20 percent were reported in all regions for ampicillin and in many regions for trimethoprim (with or without sulfamethoxazole).

Nitrofurantoin, fosfomycin, and pivmecillinam (the last is not available in the United States) have demonstrated good in vitro activity in all countries investigated [16-19] and are thus appropriate first-line agents for acute simple cystitis when there are no clear risk factors for resistance [1].

Resistance rates for first and second generation oral cephalosporins and amoxicillin-clavulanic acid are regionally variable but generally <10 percent.

Fluoroquinolone resistance rates have been <10 percent in most parts of North America and Europe, but there has been a clear trend of increasing resistance over time [16-21]. In a study of *E. coli* urinary isolates from outpatients in the United States, resistance rates to ciprofloxacin increased from 3 to 17 percent between 2000 and 2010 [20]. In a population-based study of over 5000 *E. coli* urinary isolates collected in Minnesota between 2005 and 2009, the incidence of urinary isolates resistant to fluoroquinolones and/or trimethoprim-sulfamethoxazole (TMP-SMX) increased among older adult patients and those with community-associated isolates, but not among health care-associated cases [21]. One caveat in interpreting these data is that passive laboratory-based surveillance methods tend to overestimate true resistance rates since they are skewed by urine cultures obtained from patients who may have failed initial therapy or who have specific risk factors for resistance, such as recent travel or antimicrobial use [22-24].

TMP-SMX is the agent for which there are the most data to guide clinical use; identified risk factors for resistance in females with acute simple cystitis include use of TMP-SMX in the preceding three to six months and travel, particularly international travel [25-28]. In addition, clinical, in vitro, and mathematical modeling studies have suggested that a 20 percent resistance prevalence should be the threshold at which TMP-SMX should not be used for empiric treatment of acute simple cystitis [29,30].

For other antimicrobial agents, there are insufficient data to determine the resistance levels at which the likelihood of failure outweighs the potential benefits; the decision depends on individual practitioner discretion. In addition, it is important for clinicians to understand that local resistance rates reported in hospital antibiograms are often skewed by cultures of samples obtained from hospitalized patients or those with complicated infection and may

not accurately predict susceptibilities in females with acute simple community-acquired cystitis, in whom resistance rates tend to be lower [31,32].

Nevertheless, resistant infections are increasing in number, including those caused by extended-spectrum beta-lactamase (ESBL)-producing strains. An increase in ESBL-producing isolates has been described among patients with acute simple cystitis worldwide [33-35]. In particular, a specific strain of *E. coli*, sequence type 131 (ST131), has emerged globally as a major cause of fluoroquinolone-resistant and ESBL-producing *E. coli* UTIs [36].

CLINICAL MANIFESTATIONS

The classic clinical manifestations of cystitis consist of dysuria, urinary frequency, urinary urgency, and suprapubic pain [37]. Hematuria is also often observed.

Symptoms of cystitis can occasionally be subtle and more difficult to tease out, particularly in older females. Older females can have a number of nonspecific urinary symptoms (such as chronic dysuria or urinary incontinence) that mimic symptoms of cystitis, even when there is no evidence of urinary tract infection (UTI). A systematic review of studies evaluating the diagnosis of UTI among community-dwelling adults older than 65 years suggested that symptoms such as chronic urinary nocturia, incontinence, and general sense of lack of well-being were common and nonspecific for UTI [38]. In contrast, acute dysuria (less than one week duration), new or worsening urinary urgency, new incontinence, frequency, gross hematuria, and suprapubic pain or tenderness were more discriminating symptoms. Fever was also a discriminating feature, although we consider patients with cystitis symptoms and fever to have a complicated UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Clinical manifestations'.)

Similarly, among debilitated patients, many generalized signs or symptoms, such as falls, change in functional status, and change in mental status, are frequently attributed to UTI, but growing evidence indicates that these are not reliable predictors of bacteriuria or cystitis. In one cohort study of nursing home residents, among clinical features that prompted evaluation for UTI (including change in gait or falls, change in functional status, fever or chills), only acute dysuria, change in the character of urine (gross hematuria, change in color or odor), and change in mental status were associated with the presence of both pyuria and bacteriuria [39]. However, other studies that controlled for comorbidities have found no association between bacteriuria in nursing home patients and nonspecific mental status changes (such as increased restlessness, confusion, or aggression) [40]. Among those with bacteriuria, there also appears to be no association between these nonspecific mental status changes and urinary markers of inflammation (ie, interleukin-6) [41]. Furthermore, treatment of bacteriuria in patients with acute delirium or nonspecific symptoms is not

associated with improvement in mental or functional status (but is associated with *Clostridioides* [formerly *Clostridium*] *difficile* infection) [42,43].

Although cloudy or smelly urine may be associated with bacteriuria (as demonstrated in nursing home residents [39]), there is no evidence of benefit to treating patients with only these complaints as having a UTI prior to onset of usual cystitis symptoms. Color and odor of urine are influenced by ingestion of certain foods, dehydration, and other noninfectious factors. Thus, increased fluid intake and careful observation are reasonable initial approaches to patients who complain of changes in odor or color of urine.

Fever, chills, rigors, and other signs of systemic illness are not compatible with a diagnosis of acute simple cystitis and raise the possibility of pyelonephritis or other complication of UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults".)

DIAGNOSTIC APPROACH

Clinical suspicion and evaluation — Acute simple cystitis should be suspected in females who have acute symptoms of dysuria, urinary frequency or urgency, and/or suprapubic pain, particularly in the absence of vaginal symptoms (eg, vaginal pruritus or discharge). The probability of cystitis is greater than 50 percent in females with any of these symptoms and greater than 90 percent in females who have dysuria and frequency without vaginal discharge or irritation [37].

Females should be asked about fevers/chills and flank pain. Physical examination is often not necessary for the diagnosis, but if performed, should include assessment for fever, costovertebral angle tenderness, and abdominal tenderness. A pelvic examination is indicated if symptoms or signs suggesting vaginitis or urethritis are present. If fever (>99.9°F/37.7°C), other signs or symptoms of systemic illness (including chills, rigors, or marked fatigue or malaise beyond baseline), flank pain, or costovertebral angle tenderness are present, the patient should be evaluated and managed as potentially having complicated urinary tract infection (UTI), which is discussed in detail elsewhere. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults".)

For most females with suspected acute simple cystitis, particularly those with classic symptoms, no additional testing is warranted to make the diagnosis.

However, in females who have clinical features that are suggestive, but not clearly diagnostic of cystitis (such as atypical urinary symptoms), urinalysis is a useful diagnostic tool, as the absence of pyuria on urinalysis suggests a diagnosis other than cystitis. Apart from the classic features listed above, features that should prompt urine testing include new or worsening urinary urgency, new incontinence, or gross hematuria. Chronic urinary nocturia,

chronic incontinence, general malaise, and cloudy or malodorous urine are nonspecific findings that should not routinely prompt urine testing to evaluate for cystitis. We do not routinely test urine in elderly or debilitated patients with nonspecific changes in mental or functional status in the absence of focal urinary tract symptoms, and instead hydrate, carefully observe, and assess other potential contributing factors [44]. If fever is also present, evaluation for infection, including complicated UTI, is warranted (see "Acute complicated urinary tract infection (including pyelonephritis) in adults"). The evaluation and diagnosis of UTI in elderly adults is further discussed elsewhere. (See "Approach to infection in the older adult", section on 'Urinary tract infection'.)

When indicated, urinalysis can be performed either by microscopy or by dipstick. (See 'Urinalysis' below.)

Urine culture and susceptibility testing are also generally unnecessary in females with acute simple cystitis, but should be performed in patients who are at risk for infection with a resistant organism (table 2). We also check culture and susceptibility testing on patients with risk factors for more serious infection, such as those with underlying urologic abnormalities, immunocompromising conditions, and poorly controlled diabetes, regardless of other risk factors for resistance. (See 'Determining the microbial etiology' below.)

Pregnancy testing is appropriate in individuals of childbearing potential when the possibility of pregnancy cannot be reasonably excluded by history alone.

Blood testing is not warranted for patients with acute simple cystitis.

Urinalysis — Urinalysis (either by microscopy or by dipstick) for evaluation of pyuria is a valuable laboratory diagnostic test for UTI. It is not indicated in females with typical symptoms of acute simple cystitis (in whom the diagnosis can reliably be made on symptoms alone), but it can be helpful in cases in which the clinical presentation is not typical. Pyuria is present in almost all females with acute cystitis; its absence strongly suggests an alternative diagnosis [45,46].

- The most accurate method for assessing pyuria is to examine an unspun, voided midstream urine specimen under the microscope with a hemocytometer; an abnormal result is ≥10 leukocytes/microL [45]. However, this laboratory test is usually not available to the clinician. The presence of hematuria is helpful since it is common in the setting of UTI but not in urethritis or vaginitis. However, hematuria is not a predictor for complicated infection and does not alter the approach to therapy. White blood cell casts in the urine, although rare, are indicative of upper tract infection rather than simple cystitis. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Diagnostic approach'.)

- Dipsticks are commercially available strips that detect the presence of leukocyte esterase (an enzyme released by leukocytes, reflecting pyuria) and nitrite (reflecting the presence of Enterobacteriaceae, which convert urinary nitrate to nitrite). The dipstick test is most accurate for predicting UTI when positive for either leukocyte esterase or nitrite, with a sensitivity of 75 percent and a specificity of 82 percent [37]. However, results of the dipstick test provide little useful information when the clinical history is strongly suggestive of UTI, since even negative results for both tests do not reliably rule out infection in such cases.

Additional details on urine collection and testing (with microscopy for pyuria and dipstick) are found elsewhere. (See "Sampling and evaluation of voided urine in the diagnosis of urinary tract infection in adults".)

Determining the microbial etiology — The causative organisms and their antimicrobial susceptibility profiles are frequently predictable in females with acute simple cystitis, and thus routine cultures for such infections are often not necessary for management decisions. However, given the increasing prevalence of antimicrobial resistance among uropathogens, obtaining a urine culture prior to initiation of therapy is warranted in patients who have risk factors for antimicrobial resistance (table 2), as well as in patients at risk for more serious infection (eg, those with underlying urologic abnormalities, immunocompromising conditions, and poorly controlled diabetes mellitus).

If voided urine cultures are sent to the laboratory, the clinician should ask the laboratory to quantify *E. coli*, if it grows, to at least 10^3 colony-forming units/mL to improve specificity. Moreover, *E. coli* should not necessarily be considered a contaminant if it grows in mixed flora since almost any growth of *E. coli* in voided urine in a symptomatic patient reflects bladder growth [10]. Growth of organisms generally thought to be contaminants (such as lactobacilli, enterococci, Group B streptococci, and non-saprophyticus coagulase-negative staphylococci) may be considered causative when found in voided midstream urine at high counts and with pure growth (see 'Microbiology' above). Issues related to interpretation of urine culture colony counts are discussed separately. (See "Sampling and evaluation of voided urine in the diagnosis of urinary tract infection in adults", section on 'Definition of a positive culture'.)

Diagnosis — The clinical diagnosis of cystitis is made in a patient who has classic signs and symptoms (ie, dysuria, urinary frequency, urgency, and/or suprapubic pain). For females who have atypical urinary symptoms, the diagnosis is supported by the presence of pyuria and bacteriuria on urinalysis and/or culture. (See 'Clinical suspicion and evaluation' above.)

The clinical diagnosis of acute **simple** cystitis also excludes fever (>99.9°F/37.7°C), other signs or symptoms of systemic illness (including chills, rigors, or marked fatigue or malaise beyond baseline), flank pain, and costovertebral angle tenderness (table 1). The presence

of any of these features suggests pyelonephritis or extension of the infection beyond the bladder, and we thus consider the patient to have an acute **complicated** UTI, which is discussed in detail elsewhere. We also have a lower threshold to consider patients with risk factors for more serious infection as having acute complicated UTI, for example, if they have more subtle signs or symptoms of possible upper tract or systemic infection. Such risk factors include urologic abnormalities (eg, nephrolithiasis, strictures, stents, or urinary diversions), immunocompromising conditions (eg, neutropenia or advanced HIV infection), or poorly controlled diabetes mellitus. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults".)

Bacteriuria with or without pyuria in the absence of any symptom that could be attributable to a UTI is called asymptomatic bacteriuria and generally does not warrant treatment in nonpregnant patients who are not undergoing urologic procedures. (See "Asymptomatic bacteriuria in adults".)

The diagnosis of UTI in a patient with an indwelling urinary catheter is discussed in further detail elsewhere. (See "Catheter-associated urinary tract infection in adults", section on 'Diagnosis'.)

DIFFERENTIAL DIAGNOSIS

Both infectious and noninfectious processes can cause symptoms of dysuria, frequency, urgency, suprapubic pain, and/or hematuria [9].

- Vaginitis – In females with dysuria, the presence of vaginal discharge or odor, pruritus, dyspareunia, and absence of urinary frequency or urgency should prompt consideration of vaginitis. Causes of vaginitis include yeast infection, trichomoniasis, and bacterial vaginosis. (See "Vaginal discharge (vaginitis): Initial evaluation".)

- Urethritis – Evaluation for urethritis is warranted in sexually active females with dysuria, particularly those with pyuria on urinalysis but no bacteriuria. Causes of urethritis in females include chlamydia, gonorrhea, trichomoniasis, *Candida* species, herpes simplex virus, and noninfectious irritants, such as a contraceptive gel. (See "Clinical manifestations and diagnosis of Chlamydia trachomatis infections", section on 'Dysuria-pyuria syndrome due to urethritis'.)

- Painful bladder syndrome – This is a diagnosis of exclusion in females who have ongoing discomfort related to the bladder with symptoms of dysuria, frequency, and/or urgency but no evidence of infection or other identifiable cause. (See "Interstitial cystitis/bladder pain syndrome: Clinical features and diagnosis".)

- Pelvic inflammatory disease – Lower abdominal or pelvic pain and fever are the most common clinical findings in patients with pelvic inflammatory disease (PID), although dysuria may also be present. The findings of mucopurulent endocervical discharge or cervical motion tenderness on pelvic examination are strongly suggestive of PID. (See "Pelvic inflammatory disease: Clinical manifestations and diagnosis".)

MANAGEMENT

Empiric antimicrobial selection — The selection of an antimicrobial regimen for acute simple cystitis (table 1) depends on the risk of infection with a multidrug-resistant (MDR) gram-negative organism (algorithm 1).
(Related Pathway(s): Urinary tract infection (UTI): Empiric antibiotic selection for acute simple cystitis in female adults.)

We generally consider patients to be higher risk for an MDR gram-negative organism if they have any of the following occurring in the prior three months:

- An MDR gram-negative urinary isolate (ie, nonsusceptible to at least one agent in three or more antimicrobial classes; this includes extended-spectrum beta-lactamase [ESBL]-producing isolates).
- Inpatient stay in a health care facility (eg, hospital, nursing home, long-term acute care facility).
- Use of a fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam (eg, third or later generation cephalosporin) [47].
- Travel to parts of the world with high rates of MDR organisms (eg, India, Israel, Spain, Mexico).

Females categorized as having acute uncomplicated cystitis according to the traditional definition would fall under the definition of acute simple cystitis that we use here and be managed as presented here. (See 'Terminology' above.)

Low risk for resistance — For patients who do not have risk factors for an MDR gram-negative infection (table 2), we typically choose one of the first-line antimicrobial regimens (nitrofurantoin monohydrate/macrocrystals, trimethoprim-sulfamethoxazole, fosfomycin, or pivmecillinam) (algorithm 1). (See 'First-line antimicrobial options' below.)

For patients who have reasons to avoid all these options (either because of allergies or intolerances or a history of a urinary isolate resistant to these agents within the prior three months), we choose an alternative option. (See 'Alternative antimicrobial options' below.)

First-line antimicrobial options — The preferred agents for empiric therapy of acute simple cystitis are nitrofurantoin monohydrate/macrocrystals, trimethoprim-

sulfamethoxazole, fosfomycin, and, if available, pivmecillinam because of the favorable balance between efficacy and adverse effects (including the risk of selecting for resistant organisms) [1]. None of the first-line agents clearly outweighs the others in terms of the efficacy/adverse effects balance, with the exception that resistance is more likely with trimethoprim-sulfamethoxazole and that pivmecillinam (and possibly fosfomycin) is somewhat less effective; the optimal antimicrobial in one region may be different from that in another depending on resistance prevalence (see 'Resistance trends in E. coli' above). Thus, the choice among them should be individualized based on patient circumstances (allergy, tolerability, expected adherence), local community resistance prevalence, availability, cost, and patient and provider threshold for failure. If the patient has taken one of the agents in the preceding three months, a different one should be selected.

If all these are appropriate options based on patient circumstances and prior urinary isolates, we suggest nitrofurantoin or trimethoprim-sulfamethoxazole rather than fosfomycin or pivmecillinam. Because fosfomycin retains activity against many MDR isolates and overuse may result in increasing rates of resistance, we favor reserving it for suspected MDR infections or when other first-line agents cannot be used. Pivmecillinam is somewhat less effective but is commonly used in Europe because of a low risk of selection for resistance.

Details on dosing, expected efficacy, and additional reasons for avoidance are as follows:

- **Nitrofurantoin monohydrate/macrocrystals (Macrobid)** – Dosed at 100 mg orally twice daily for five days. Randomized trials suggest a 79 to 92 percent clinical cure rate with a five- to seven-day regimen, with minimal resistance promotion [48-50]. Higher rates of failure occurred with shorter courses [51]. It has minimal propensity to select for resistant organisms. Nitrofurantoin should be avoided if there is suspicion for early pyelonephritis or if the creatinine clearance is <30 mL/minute. Observational studies have suggested that the agent is effective and safe with mild renal impairment, even in older females [52-55].

- **Trimethoprim-sulfamethoxazole** – Dosed as one double-strength tablet (160/800 mg) orally twice daily for three days. Randomized trials suggest a 79 to 100 percent clinical cure rate with a three- to seven-day regimen [48,56-58]. Empiric trimethoprim-sulfamethoxazole should be avoided if the regional prevalence of resistance is known to exceed 20 percent [29,30]. In some regions, trimethoprim (100 mg twice daily for three days) is used in place of trimethoprim-sulfamethoxazole and is considered equivalent [59].

- **Fosfomycin** – Dosed as 3 g of powder mixed in water as a single oral dose. One randomized trial reported an early clinical cure rate of 91 percent and a bacterial cure rate similar to nitrofurantoin [60], and a meta-analysis demonstrated no difference in

cure rates between fosfomycin and other agents, including fluoroquinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin [61]. However, in a subsequent open-label trial, a single dose of fosfomycin resulted in lower clinical (58 versus 70 percent) and microbiologic (63 versus 74 percent) success rates at 28 days compared with nitrofurantoin given three times daily for five days [62]. Lower than expected clinical success rates in both groups may be a result of the definition used in this study (complete resolution of UTI signs and symptoms rather than improvement of signs and symptoms, as used in other trials). It is not clear whether the open-label trial design influenced the findings [63]. Susceptibility testing for fosfomycin is not routinely available in most clinical laboratories. Fosfomycin should be avoided if there is suspicion for early pyelonephritis.

- **Pivmecillinam** – Doses used in studies range from 400 mg orally two or three times daily for three to seven days; we suggest a dose of 400 mg three times daily for three to five days. In one randomized trial of females with cystitis, the 400 mg three times daily dose given for three versus five days resulted in similarly high clinical (73 versus 76 percent) and microbiologic success rates (87 versus 88 percent) [64]. Pivmecillinam is a penicillin with an extended gram-negative spectrum, is used only for treatment of urinary tract infection (UTI) and has minimal propensity to select for resistant organisms [65,66]. It is not available in the United States but is an agent of choice in many Nordic countries due to low resistance rates [67]. Pivmecillinam should be avoided if there is suspicion for early pyelonephritis.

These antimicrobial options and suggested treatment durations for acute simple cystitis are the same for any adult woman with acute simple cystitis, regardless of age [68]. A systematic review of studies evaluating treatment of cystitis in community-dwelling adults ≥65 years of age concluded that the optimal regimens are the same as those recommended for younger adults and that shorter antimicrobial courses (three to six days) resulted in similar outcomes as longer ones (7 to 14 days) [69]. However, since these studies excluded females with urinary tract abnormalities, immunocompromising conditions, or poorly controlled diabetes mellitus, it is reasonable to use a longer duration of therapy (eg, 7 days) in females with such comorbidities.

If there is diagnostic uncertainty regarding cystitis versus early pyelonephritis, we treat the patient as having an acute complicated UTI (which includes pyelonephritis). In particular, the use of nitrofurantoin, fosfomycin, and pivmecillinam should be avoided in such cases because they do not achieve adequate renal tissue levels [1]. This is discussed in detail elsewhere. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Management'.)

Alternative antimicrobial options — If any factors (such as allergies or concern for resistance) preclude use of the above first-line antimicrobials, oral beta-lactams (other than pivmecillinam) are appropriate options, and if beta-lactams cannot be used, a fluoroquinolone is reasonable (algorithm 1).

Acceptable beta-lactam agents include amoxicillin-clavulanate (500 mg twice daily), cefpodoxime (100 mg twice daily), cefdinir (300 mg twice daily), and cefadroxil (500 mg twice daily), each given for five to seven days [58,70,71]. A shorter course is not adequate; in one trial, cefpodoxime did not meet criteria for noninferiority to ciprofloxacin for clinical cure when each was given for three days [72]. Other beta-lactams, such as cephalexin (250 to 500 mg every six hours), are less well studied but may be acceptable. Ampicillin or amoxicillin should **not** be used for empiric treatment given the high prevalence of resistance to these agents [16-19,59]. In general, beta-lactams are second-line agents because they are less effective and have more potential adverse effects than other UTI antimicrobials [59,71,73,74].

If beta-lactams cannot be used (eg, because of severe allergy), ciprofloxacin (250 mg twice daily or 500 mg extended release daily) and levofloxacin (250 mg daily), each for three days, are reasonable alternative agents. Other less commonly used fluoroquinolones that are effective include ofloxacin and norfloxacin. Moxifloxacin attains lower urinary levels than other fluoroquinolones and should not be used. Multiple randomized trials have demonstrated that fluoroquinolones are very effective for treatment of acute cystitis, and that fluoroquinolones are more effective than beta-lactams [57,66,70,71,75-80]. However, increasing rates of resistance mitigate the utility of the fluoroquinolone class. Furthermore, because of concerns about the adverse effects of fluoroquinolones, the risk-benefit balance for acute cystitis favors the use of fluoroquinolones only if other agents (including beta-lactams) cannot be used. When possible, fluoroquinolones should be reserved for more serious infections than acute simple cystitis [81,82]. If a fluoroquinolone is used, patients should be advised about the uncommon but potentially serious musculoskeletal and neurologic adverse effects. (See "Fluoroquinolones", section on 'Benefits and risks of use'.)

If a patient has reasons not to use any of the first-line agents, beta-lactams, or fluoroquinolones, we obtain urine culture and susceptibility testing and select an antimicrobial based on those results (see 'Directed antimicrobial selection' below). For acute simple cystitis, studies among females without comorbidities have suggested that deferring antimicrobial therapy until these results are available is a safe strategy [83]. Analgesics can be used for symptomatic therapy in the interim for females with mild to moderate symptoms (see 'Symptomatic therapy' below). If there are concerns about deferring antimicrobials (eg, because of significant bladder symptoms), it is reasonable to treat empirically with an agent (eg, first-line option, beta-lactam, or fluoroquinolone) that was initially avoided because of concerns for possible resistance while awaiting culture results.

Alternately, if there are concerns about potential treatment failure with oral agents in patients with risk factors for more serious infection (eg, an underlying urologic condition or immunocompromising condition), the patient can be treated with an initial intravenous agent, as in our approach to complicated UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Outpatients'.)

High risk for resistance — For patients who have risk factors for an MDR gram-negative infection (table 2), we first obtain urine culture and susceptibility testing (algorithm 1). For empiric treatment, oral options include nitrofurantoin monohydrate/macrocrystals (Macrobid, 100 mg orally twice daily for five days), fosfomycin (3 g of powder mixed in water as a single dose), or, if available, pivmecillinam (400 mg orally three times daily for three to five days), unless the patient has a history of an isolate with documented resistance to these agents in the prior three months. If all these are appropriate options based on patient circumstances (allergies, intolerances, drug interactions) and prior urinary isolates, we suggest nitrofurantoin. We favor reserving the use of fosfomycin for documented MDR gram-negative infections or when nitrofurantoin is not an option, and pivmecillinam is not as effective. In the United States, resistance to all oral options is still uncommon among outpatients with *E. coli* cystitis.

Studies have suggested that nitrofurantoin, fosfomycin, and pivmecillinam still retain clinical activity against some MDR organisms, including ESBL-producing isolates [35,73,84,85]. As an example, in a case-control study including 113 patients with ESBL-producing *E. coli* UTIs, no resistance to fosfomycin was detected and clinical cure rates were high (93 percent) [73]. Some studies have evaluated a higher dose of fosfomycin (eg, 3 g once every 2 to 3 days for 3 doses) for infections due to MDR organisms, but there is no evidence that this has greater efficacy than single-dose therapy [86,87].

If none of these can be used because of resistance or other concerns, we defer antimicrobial therapy until a regimen can be selected based on results of culture and susceptibility testing (see 'Directed antimicrobial selection' below). For acute simple cystitis, studies among females without comorbidities have suggested that deferring antimicrobial therapy until these results are available is a safe strategy [83]. Analgesics can be used for symptomatic therapy in the interim for females with mild to moderate symptoms (see 'Symptomatic therapy' below). If there are concerns about deferring antimicrobials (eg, because of significant bladder symptoms), it is reasonable to treat empirically with an agent (eg, first-line option, beta-lactam, or fluoroquinolone) that was initially avoided because of concerns for possible resistance while awaiting culture results. Alternately, if there are concerns about potential treatment failure with oral agents in patients with risk factors for more serious infection (eg, an underlying urologic condition or immunocompromising condition), the patient can be treated with an initial intravenous agent, as in our approach to complicated

UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Outpatients'.)

Directed antimicrobial selection — Acute simple cystitis in females is often treated empirically without culture and susceptibility testing. If such testing was performed (eg, because of risk for resistance or severe infection), those results can be used to inform regimen selection or adjustment. If susceptibility of the isolate allows, the approach to antimicrobial selection generally follows the same preferences as for empiric antimicrobial regimen selection, with nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, and, if available, pivmecillinam as the preferred agents, followed by beta-lactams, followed by fluoroquinolones. The doses and durations for each option are detailed elsewhere. (See 'First-line antimicrobial options' above and 'Alternative antimicrobial options' above.)

If an *Enterococcus* or Group B *Streptococcus* grows as the only isolate on culture and is determined to be the cause of cystitis (see 'Determining the microbial etiology' above), amoxicillin (500 mg orally every eight hours or 875 mg twice daily for five days) is usually the preferred agent, as long as the isolate is susceptible. (See "Treatment of enterococcal infections", section on 'Urinary tract infection' and "Group B streptococcal infections in nonpregnant adults", section on 'Regimen selection'.)

If the patient cannot use any of the above options because of expected resistance or allergies to antibiotics, options are limited. In patients who have severe or highly bothersome symptoms, the most reliable approach is to treat with a parenteral agent (for at least the first dose), as for acute complicated UTI. Such regimens are discussed elsewhere. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Outpatients'.)

However, for patients with milder symptoms, it is reasonable to try to treat with oral agents of uncertain efficacy with or without analgesic rather than proceed to a parenteral agent. As an example, if the isolate is susceptible to doxycycline, a trial of that agent is reasonable, although data in UTI are sparse [88]. Otherwise, even if an isolate is resistant to trimethoprim-sulfamethoxazole or a fluoroquinolone, using one of these still has the potential to be effective since these agents obtain high levels in the urine. Alternatively, deferring therapy for mild symptoms is also a reasonable approach for amenable patients, as symptoms can resolve spontaneously in some.

Antimicrobial sparing strategies — Given that acute simple cystitis is associated with increasing antimicrobial resistance and has a low risk of progression to invasive disease in patients without risk factors for serious infection, antimicrobial sparing management strategies (eg, anti-inflammatory drugs or delayed treatment) for some females with simple cystitis are of increasing interest but warrant further study before they can be routinely employed [83,89,90].

Delaying antimicrobial therapy while awaiting urine culture results appears to be a reasonable approach in females without comorbidities if empiric therapy is complicated by resistance or drug intolerance. In a randomized trial of nonpregnant females <75 years of age with acute simple cystitis, symptom duration and severity were similar with immediate antimicrobial therapy compared with four other strategies, including delayed antimicrobial therapy and antimicrobial therapy based on a symptom score, urinalysis findings, or urine culture results [83]. In a systematic review of three trials of cystitis, approximately one-third of those in the placebo or no treatment group had symptom resolution by seven days [91]. Although a large retrospective database analysis of patients ≥65 years of age with lower urinary tract infection suggested an association between delaying antimicrobial therapy and subsequent bloodstream infection within 60 days, multiple limitations of this study reduce confidence in the findings; these include potential misdiagnosis of cystitis, important and potentially confounding differences between groups, and failure to link the microbiology of the cystitis to bacteremia [92].

Substituting anti-inflammatory agents for antimicrobial therapy has also been evaluated but, pending additional data, cannot be recommended as an initial approach to management of symptomatic acute simple cystitis. In one trial of 241 females with acute simple cystitis without risk factors for complications, those randomly assigned to treatment with ibuprofen (400 mg three times daily for three days) had a higher mean symptom burden compared with those who received fosfomycin as a single 3 g dose [90]. Fewer females in the ibuprofen group received any antimicrobials compared with the fosfomycin group (35 versus 100 percent), but they were more likely to require additional therapy with antimicrobials in follow-up and had a higher rate of serious adverse events, including five cases of pyelonephritis (2 percent) compared with one case (0.4 percent) in the fosfomycin group. Similar findings were observed in a trial comparing diclofenac with norfloxacin [93].

Other interventions

Symptomatic therapy — Symptoms of acute simple cystitis should respond to antimicrobial therapy within 48 hours. In fact, dysuria is usually diminished within a few hours after the start of antimicrobial therapy [94]. In the interim, for some patients with severe dysuria, a urinary analgesic such as over-the-counter oral phenazopyridine three times daily as needed may be useful to relieve discomfort. A two-day course is usually sufficient to allow time for symptomatic response to antimicrobial therapy and minimize inflammation. Phenazopyridine should not be used chronically since it may mask clinical symptoms requiring clinical evaluation.

Patients with urologic abnormalities — In many cases, patients with underlying functional or anatomic urinary tract abnormalities (such as an indwelling catheter, urethral stent, neurogenic bladder, nephrolithiasis) have systemic symptoms (such as fever or

autonomic dysreflexia) in the setting of UTI and are thus managed as having a complicated UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Management'.)

For those who appear to have only acute simple cystitis without upper tract or systemic symptoms, we believe that it is reasonable to cautiously treat them as outlined above. However, because these patients were not included in efficacy studies of the regimens we use for simple cystitis, we monitor them carefully for treatment failure (eg, persistent symptoms after initiation of empiric therapy) and follow initial urine cultures to ensure that the empirically chosen regimen was appropriate. Furthermore, since the antimicrobial durations listed above have not been well studied in patients with urologic dysfunction, a longer duration of therapy (eg, one to two weeks, depending on the agent chosen) is reasonable. It is also reasonable to have a lower threshold to treat such patients as having a complicated UTI (eg, for more subtle symptoms of pyelonephritis or systemic infection).

In addition, other treatment measures in addition to antimicrobial therapy may be warranted. These include more frequent intermittent catheterization, changing out an indwelling catheter prior to obtaining a urine culture (particularly if it has been in place for longer than one or two weeks), or urologic/urogynecologic consultation.

FOLLOW-UP

Follow-up urine cultures are not needed in patients with acute simple cystitis whose symptoms resolve on antimicrobials. For patients who had hematuria on initial presentation, a urinalysis should be repeated several weeks following antimicrobial therapy to evaluate for persistent hematuria. (See "Etiology and evaluation of hematuria in adults", section on 'Overall approach to the evaluation'.)

Patients who have persistent symptoms after 48 to 72 hours of empiric antimicrobial therapy or have recurrent symptoms within a few weeks of treatment should have additional evaluation for other potential conditions that may be causing those symptoms and for factors that might be compromising clinical response. This includes urine culture and empiric treatment with another antimicrobial agent. Subsequent treatment should be tailored to the susceptibility profile of the causative organism isolated (see 'Directed antimicrobial selection' above). If symptoms persist in the setting of appropriate antimicrobial therapy, urologic assessment and radiographic imaging (generally with computed tomography) may be appropriate to evaluate for anatomic abnormalities that would interfere with response to antimicrobial treatment.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Urinary tract infections in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Urinary tract infections in adults (The Basics)")
- Beyond the Basics topic (see "Patient education: Urinary tract infections in adolescents and adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Terminology** – We use the term “acute simple cystitis” to refer to an acute infection that is confined to the bladder in a nonpregnant individual (table 1). Such infections lack features that suggest infection extends beyond the bladder, such as fever (>99.9°F/37.7°C), other signs or symptoms of systemic illness (including chills, rigors, and marked fatigue or malaise beyond baseline), flank pain, and costovertebral angle tenderness.

  This definition is distinct from traditional categorizations of urinary tract infection (UTI) and is more focused on the clinical presentation and severity of illness. Females categorized as having acute uncomplicated cystitis according to traditional definitions would fall under the definition of acute simple cystitis that we use here. (See 'Terminology' above.)

- **Microbiology** – *Escherichia coli* is the most frequent microbial cause of cystitis, with occasional infections caused by other species of Enterobacteriaceae, such as *Klebsiella*

pneumoniae and *Proteus mirabilis*, and other bacteria, such as *Staphylococcus saprophyticus.* The microbial spectrum of cystitis in patients with recent antimicrobial or other health care exposures may be broader and also include other gram-negative bacilli (eg, *Pseudomonas*), enterococci, and staphylococci. Increasing rates of resistance in uropathogens have been reported globally. Risk factors for UTI with resistant organisms include recent antimicrobial use, health care exposures, and travel to parts of the world where multidrug-resistant (MDR) organisms are prevalent (table 2). (See 'Microbiology' above.)

- **Clinical suspicion and diagnosis** – In females with classic symptoms of dysuria, urinary frequency, urinary urgency, and suprapubic pain, the diagnosis of cystitis can usually be made on clinical presentation alone without additional testing. Older or debilitated females can have nonspecific urinary symptoms (such as chronic dysuria or urinary incontinence) that mimic symptoms of cystitis and are difficult to distinguish from them. In such cases, we check a urinalysis and urine culture and make the diagnosis of cystitis if pyuria and bacteriuria are present. Chronic nocturia, chronic incontinence, general malaise, and cloudy or malodorous urine are nonspecific findings that should not routinely prompt urine testing to evaluate for cystitis. (See 'Clinical suspicion and evaluation' above and 'Diagnosis' above.)

  Fever, systemic symptoms, and flank pain or tenderness in a patient with symptoms of cystitis, pyuria, and bacteriuria are suggestive of complicated UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Clinical manifestations'.)

- **Asymptomatic bacteriuria** – In the absence of consistent urinary symptoms, bacteriuria (with or without pyuria) is **not** diagnostic of cystitis. (See "Asymptomatic bacteriuria in adults".)

- **Empiric antimicrobial selection** – The selection of an antimicrobial regimen for acute simple cystitis depends on the likelihood of infection with an MDR gram-negative isolate (algorithm 1). Prior to initiation of therapy, urine culture and susceptibility testing are warranted for patients who have risk factors for antimicrobial resistance (table 2) or for more serious infection (eg, those with underlying urologic abnormalities, immunocompromising conditions, and poorly controlled diabetes mellitus). (See 'Empiric antimicrobial selection' above.)
  (Related Pathway(s): Urinary tract infection (UTI): Empiric antibiotic selection for acute simple cystitis in female adults.)

  - **Patients without risk factors for MDR gram-negative infection** (table 2) – For such patients, the first-line antimicrobial agents include:

- Nitrofurantoin monohydrate/macrocrystals (Macrobid, 100 mg twice daily for five days)
- Trimethoprim-sulfamethoxazole (one double-strength tablet [160/800 mg] twice daily for three days)
- Fosfomycin (3 g of powder mixed in water as a single dose)
- Pivmecillinam (400 mg twice daily for five to seven days).

If all these are appropriate options based on patient circumstances, local resistance rates, and prior urinary isolates, we suggest nitrofurantoin or trimethoprim-sulfamethoxazole rather than fosfomycin or pivmecillinam (**Grade 2C**). (See 'First-line antimicrobial options' above.)

Oral beta-lactams are appropriate alternative options for those who cannot use any of the first-line antimicrobials. If beta-lactams cannot be used, a fluoroquinolone is reasonable; however, these should be reserved for more serious infections than acute simple cystitis, if possible, because of concerns of adverse effects. (See 'Alternative antimicrobial options' above.)

- **Patients with risk factors for an MDR gram-negative infection** (table 2) – For such patients, oral options include nitrofurantoin monohydrate/macrocrystals (Macrobid, 100 mg orally twice daily for five days), fosfomycin (3 g of powder mixed in water as a single dose), or, if available, pivmecillinam (400 mg orally three times daily for three to five days) unless the patient has a history of an isolate with documented resistance to these agents in the prior three months. If all these are appropriate options based on patient circumstances, local resistance rates, and prior urinary isolates, we suggest nitrofurantoin (**Grade 2C**). Culture and susceptibility results should be used to guide directed therapy. (See 'High risk for resistance' above.)

- **If no oral option seems appropriate** – If none of the above options are appropriate because of resistance or other concerns, we defer antimicrobial therapy until a regimen can be selected based on results of culture and susceptibility testing. For acute simple cystitis, studies among females without comorbidities have suggested that deferring antimicrobial therapy until these results are available is a safe strategy. However, if there is concern about deferring antimicrobial therapy (eg, because of bothersome symptoms or risk factors for more serious infection), options include using one of the oral regimens for simple cystitis that was not chosen because of the possibility of resistance or using an initial dose of a parenteral agent, as used in acute complicated UTI. (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Outpatients'.)

- **Adjunctive interventions** – Patients who have acute simple cystitis in the setting of underlying functional or anatomic urinary tract abnormalities (such as an indwelling catheter, urethral stent, neurogenic bladder, history of nephrolithiasis) may warrant more frequent catheterization, changing out an indwelling catheter, or urologic/urogynecologic consultation. Additionally, a longer duration of antimicrobial therapy is appropriate, since shorter durations have not been well studied in such patients. (See 'Patients with urologic abnormalities' above.)

- **Persistent or recurrent symptoms** – Patients who have persistent symptoms after 48 to 72 hours of empiric antimicrobial therapy or have recurrent symptoms within a few weeks of treatment should have urine submitted for culture and susceptibility testing. If symptoms persist in the setting of appropriate antimicrobial therapy, radiographic imaging to evaluate for anatomic abnormalities is appropriate. (See 'Follow-up' above.)

Use of UpToDate is subject to the Terms of Use.

Topic 8063 Version 62.0

GRAPHICS

Our approach to categorizing UTI in adults and adolescents

Acute simple cystitis*	▪ Acute UTI that is presumed to be confined to the bladder ▪ There are no signs or symptoms that suggest an upper tract or systemic infection (refer to below)
Acute complicated UTI	▪ Acute UTI accompanied by signs or symptoms that suggest extension of infection beyond the bladder: • Fever (>99.9°F/37.7°C)¶ • Chills, rigors, significant fatigue or malaise beyond baseline, or other features of systemic illness • Flank pain • Costovertebral angle tenderness • Pelvic or perineal pain in men
Special populations with unique management considerations	▪ Pregnant women ▪ Renal transplant recipients

We categorize UTI as either acute simple cystitis or acute complicated UTI based on the extent and severity of infection. This categorization informs management and differs somewhat from other conventions. Specifically, cystitis or pyelonephritis in a nonpregnant premenopausal woman without underlying urologic abnormalities has traditionally been termed acute uncomplicated UTI, and complicated UTI has been defined, for the purposes of treatment trials, as cystitis or pyelonephritis in a patient with underlying urologic abnormalities or other significant comorbidities. Individuals who do not fit into either category have often been treated as having a complicated UTI by default. Rather than use this convention, we favor an approach to treatment based on the presumed extent of infection and severity of illness. Patients categorized as having acute uncomplicated cystitis according to traditional definitions would fall under the category of acute simple cystitis that we use here.

UTI: urinary tract infection.

* We do not automatically consider patients with underlying urologic abnormalities (such as nephrolithiasis, strictures, stents, or urinary diversions), immunocompromising conditions (such as neutropenia or advanced HIV infection), or poorly controlled diabetes mellitus to have a complicated UTI if they have no concerning symptoms for upper tract or systemic infection. However, such patients can be at higher risk for more serious infection and have not traditionally been included in studies evaluating the antibiotic regimens we typically use for acute simple cystitis. Thus, we follow such patients more closely and/or have a low threshold to manage them as complicated UTI (eg, if they have subtle symptoms other than those listed above that could be suggestive of more extensive infection).

¶ This temperature threshold is not well defined and should be individualized, taking into account baseline temperature, other potential contributors to an elevated temperature, and the risk of poor outcomes should empiric antimicrobial therapy be inappropriate.

Graphic 117508 Version 2.0

Risk factors for multidrug-resistant gram-negative urinary tract infections

Suspect multidrug-resistant gram-negative urinary tract infection in patients with a history of any of the following in the prior three months:
▪ A multidrug-resistant gram-negative urinary isolate or a fluoroquinolone-resistant *Pseudomonas aeruginosa* isolate
▪ Inpatient stay at a health care facility (eg, hospital, nursing home, long-term acute care facility)
▪ Use of a fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam (eg, third or later generation cephalosporin)*
▪ Travel to parts of the world with high rates of multidrug-resistant organisms¶
NOTE: The predictive value of these risk factors for multidrug-resistant gram-negative urinary tract infections has not been systematically evaluated. In particular, the time interval since these exposures is not well validated. The threshold for empirically covering a multidrug-resistant infection varies with the severity of infection, with a lower threshold warranted for more severe disease.

Multidrug resistance refers to nonsusceptibility to at least one agent in three or more antibiotic classes. This includes isolates that produce an extended-spectrum beta-lactamase (ESBL).

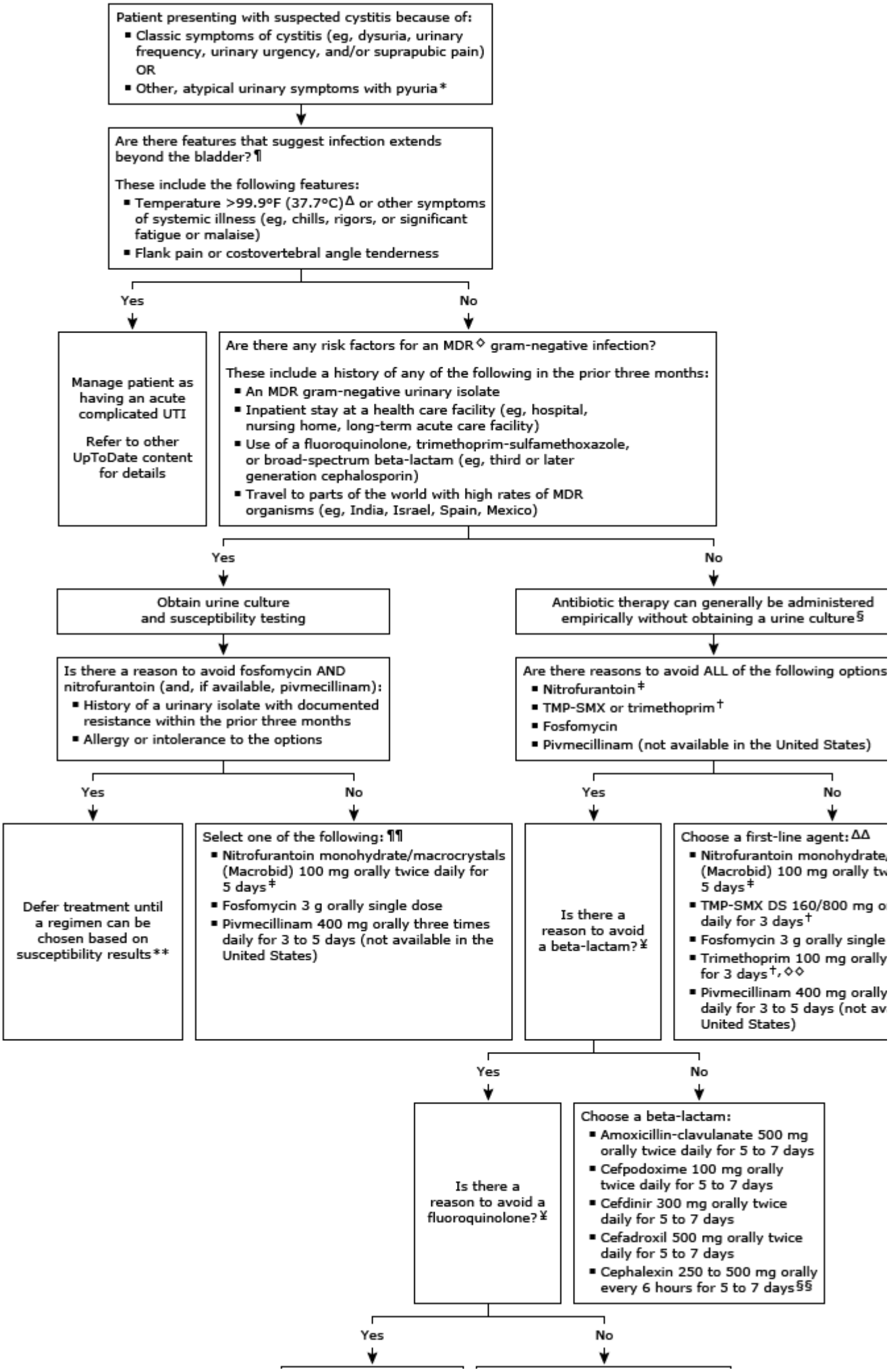
---

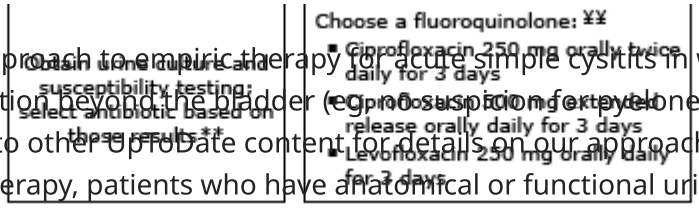
* This includes a single antibiotic dose given for prophylaxis prior to prostate procedures.

¶ The prevalence of multidrug resistance is not well documented in all parts of the world. Some countries where the prevalence is particularly high include India, Israel, Spain, and Mexico.

Graphic 114310 Version 4.0

Empiric antimicrobial selection for women with acute simple cystitis


Patient presenting with suspected cystitis because of:
Classic symptoms of cystitis (eg, dysuria, urinary frequency, urinary urgency, and/or suprapubic pain)
OR
Other, atypical urinary symptoms with pyuria*
Are there features that suggest infection extends beyond the bladder? ¶
These include the following features:
Temperature >99.9°F (37.7°C)Δ or other symptoms of systemic illness (eg, chills, rigors, or significant fatigue or malaise)
Flank pain or costovertebral angle tenderness
Yes
No
Manage patient as having an acute complicated UTI
Refer to other UpToDate content for details
Are there any risk factors for an MDR◇ gram-negative infection?
These include a history of any of the following in the prior three months:
An MDR gram-negative urinary isolate
Inpatient stay at a health care facility (eg, hospital, nursing home, long-term acute care facility)
Use of a fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam (eg, third or later generation cephalosporin)
Travel to parts of the world with high rates of MDR organisms (eg, India, Israel, Spain, Mexico)
Yes
No
Obtain urine culture and susceptibility testing
Antibiotic therapy can generally be administered empirically without obtaining a urine culture§
Is there a reason to avoid fosfomycin AND nitrofurantoin (and, if available, pivmecillinam):
History of a urinary isolate with documented resistance within the prior three months
Allergy or intolerance to the options
Are there reasons to avoid ALL of the following options
Nitrofurantoin‡
TMP-SMX or trimethoprim†
Fosfomycin
Pivmecillinam (not available in the United States)
Yes
No
Yes
No
Defer treatment until a regimen can be chosen based on susceptibility results**
Select one of the following: ¶¶
Nitrofurantoin monohydrate/macrocrystals (Macrobid) 100 mg orally twice daily for 5 days‡
Fosfomycin 3 g orally single dose
Pivmecillinam 400 mg orally three times daily for 3 to 5 days (not available in the United States)
Is there a reason to avoid a beta-lactam?¥
Choose a first-line agent: ΔΔ
Nitrofurantoin monohydrate/ (Macrobid) 100 mg orally tw 5 days‡
TMP-SMX DS 160/800 mg o daily for 3 days†
Fosfomycin 3 g orally single
Trimethoprim 100 mg orally for 3 days†,◇◇
Pivmecillinam 400 mg orally daily for 3 to 5 days (not av United States)
Yes
No
Is there a reason to avoid a fluoroquinolone?¥
Choose a beta-lactam:
Amoxicillin-clavulanate 500 mg orally twice daily for 5 to 7 days
Cefpodoxime 100 mg orally twice daily for 5 to 7 days
Cefdinir 300 mg orally twice daily for 5 to 7 days
Cefadroxil 500 mg orally twice daily for 5 to 7 days
Cephalexin 250 to 500 mg orally every 6 hours for 5 to 7 days§§
Yes
No



- This algorithm outlines the approach to empiric therapy for acute simple cystitis in women when ther concern for extension of infection beyond the bladder (eg, pyelonephritis and not a f urinary tract infection). Refer to other UpToDate content for details on our approach to categorizatio
- In addition to antimicrobial therapy, patients who have anatomical or functional urinary tract abnorm (including neurogenic bladder, indwelling bladder catheters, nephrostomy tubes, ureteral stents) ma additional management, such as more frequent catheterization to improve urinary flow, exchange of and/or urologic or gynecologic consultation.
- For each group of antibiotic options presented, the choice among them depends on patient circumst (allergy, tolerability, and adherence), susceptibility of prior urinary isolates, local community resistanc prevalence, availability, and cost. The durations presented have not been well studied in patients with tract abnormalities, immunocompromising conditions, or poorly controlled diabetes mellitus, and in patients, a longer duration of therapy (eg, 7 days) is reasonable.
- Doses listed are for patients with normal renal function and may require adjustment in the setting of impairment.

UTI: urinary tract infection; MDR: multidrug-resistant; TMP-SMX: trimethoprim-sulfamethoxazole; DS: do strength; ESBL: extended-spectrum beta-lactamase.

* Among debilitated patients, many generalized signs or symptoms, such as falls, changes in functional changes in mental status, are frequently attributed to UTI, although growing evidence indicates that the reliable predictors of bacteriuria or cystitis. We do not routinely test urine in elderly or debilitated patien nonspecific changes in mental or functional status in the absence of focal urinary tract symptoms and fe instead hydrate, carefully observe, and assess other potential contributing factors.

¶ We do not automatically consider patients with underlying urologic abnormalities (such as nephrolithi strictures, stents, or urinary diversions), immunocompromising conditions (such as neutropenia or adva infection), or poorly controlled diabetes mellitus to have a complicated UTI if they have no concerning sy for upper tract or systemic infection. However, such patients can be at higher risk for more serious infec have not traditionally been included in studies evaluating the antibiotic regimens we typically use for acu cystitis. Thus, we follow such patients more closely and/or have a low threshold to manage them as com UTI (eg, if they have subtle signs or symptoms that could be suggestive of more extensive infection).

Δ The temperature threshold used to determine whether to treat a patient as simple cystitis versus com is not well defined and should take into account baseline temperature, other potential contributors to a temperature, and the risk of poor outcomes should empiric antibiotic therapy be inappropriate.

◇ An MDR isolate is nonsusceptible to at least one agent in three or more antimicrobial classes; this incl producing isolates.

§ Even in the absence of risk factors for resistance, we also check culture and susceptibility testing on pa risk factors for more serious infection to ensure adequacy of the empirically chosen regimen. Such patie those with underlying urologic abnormalities, immunocompromising conditions, and poorly controlled d

¥ Reasons to avoid these options include an allergy or intolerance to the agent, an unmodifiable drug in or history of a resistant urinary isolate within the past three months.

‡ Nitrofurantoin should be avoided if the creatinine clearance is <30 mL/minute.

† TMP-SMX and trimethoprim should be avoided if the known community prevalence among Enterobact >20%, but efficacy is high for susceptible organisms.

** Studies have suggested that deferring antibiotic therapy until culture and susceptibility tests are avai safe strategy for otherwise healthy women who have mild simple cystitis without evidence of infection e beyond the bladder. Analgesics can be used for symptomatic therapy. If there is concern about deferring

antimicrobial therapy (eg, because of bothersome symptoms or risk factors for more serious infection), include using one of the oral regimens for simple cystitis that was not chosen because of possible resist using an initial dose of a parenteral agent, as used in acute complicated UTI.

¶¶ If all of these are appropriate options based on patient circumstances and prior urinary isolates, we f nitrofurantoin over fosfomycin. Although they appear to have generally comparable efficacy, overuse of may result in increasing resistance. Thus, we favor reserving use of fosfomycin for documented MDR inf when nitrofurantoin cannot be used. Pivmecillinam is not as effective but is commonly used in Europe b low risk of selecting for resistance.

ΔΔ If all of these are appropriate options based on patient circumstances and prior urinary isolates, we f nitrofurantoin or TMP-SMX over fosfomycin. Although they appear to have generally comparable efficac fosfomycin retains activity against many MDR isolates, and overuse of it may result in increasing resistar we favor reserving it for suspected MDR infections or when other first-line agents cannot be used. Pivm not as effective but is commonly used in Europe because of a low risk of selecting for resistance.

◇◇ Trimethoprim is an option for individuals who have a sulfonamide (but not trimethoprim) allergy.

§§ Cephalexin is not as well studied as the other beta-lactam options listed.

¥¥ When possible, fluoroquinolones should be reserved for more serious infections than acute uncompl cystitis. If used, patients should be advised about the uncommon but potentially serious musculoskelet neurologic adverse effects associated with fluoroquinolones.

Graphic 115993 Version 6.0