Acute uncomplicated cystitis and pyelonephritis in women

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INTRODUCTION — Acute cystitis refers to infection of the bladder (lower urinary tract); it can occur alone or in conjunction with pyelonephritis (infection of the kidney – the upper urinary tract). Most episodes of cystitis and pyelonephritis are generally considered to be uncomplicated in otherwise healthy nonpregnant adult women. A complicated urinary tract infection, whether localized to the lower or upper tract, is associated with an underlying condition that increases the risk of infection or of failing therapy (such as obstruction, anatomic abnormality, urologic dysfunction, or a multiply-resistant uropathogen).

Issues related to acute uncomplicated cystitis and pyelonephritis in women will be reviewed here. Issues related to urinary tract infections in men and acute complicated urinary tract infections are discussed separately. (See "Acute complicated cystitis and pyelonephritis" and "Acute uncomplicated cystitis and pyelonephritis in men").

UNCOMPPLICATED VERSUS COMPLICATED INFECTION — An uncomplicated urinary tract infection, whether localized to the lower or upper tract, is one in a patient without an underlying condition that increases the risk of failing therapy. Such conditions include:

- Poorly controlled diabetes mellitus
- Pregnancy
- Hospital-acquired infection
- Acute kidney injury or chronic kidney disease
- Suspected or known urinary tract obstruction
- Presence of an indwelling urethral catheter, stent, nephrostomy tube or urinary diversion
- Functional or anatomic abnormality of the urinary tract
- Renal transplantation
- Other immunocompromising condition (eg, chronic high-dose corticosteroid use, use of other immunosuppressive agents, neutropenia, advanced HIV infection, B or T leukocyte deficiency)

Infection with a uropathogen with broad-spectrum antimicrobial resistance is also considered complicated, although there are no data to suggest that such infections are more likely to fail if an antimicrobial to which the infecting pathogen is susceptible is used.

If any of these are present, the infection is considered a complicated urinary tract infection. These are discussed elsewhere. (See "Acute complicated cystitis and pyelonephritis").

EPIDEMIOLOGY — Among sexually active young women, the incidence of symptomatic urinary tract infection (UTI) is high; in one university cohort of 796 women, the incidence was 0.5 to 0.7 UTIs per
person-year [2]. Risk factors include recent sexual intercourse, recent spermicide use, and a history of urinary tract infection [2,3].

Cystitis also occurs in postmenopausal women. In a prospective cohort study of 1017 postmenopausal women followed for two years, the estimated incidence of culture-confirmed acute cystitis was 0.07 episodes per person per year [4].

Acute pyelonephritis is less common than acute cystitis; in one review including over 3200 patients with a first episode of acute pyelonephritis, the annual incidence of acute pyelonephritis was 12 to 13 cases per 10,000 women [5].

PATHOGENESIS — The pathogenesis of urinary tract infection in women begins with colonization of the vaginal introitus by uropathogens from the fecal flora, followed by ascension via the urethra into the bladder. Pyelonephritis develops when pathogens ascend to the kidneys via the ureters. Host and microbial factors that underlie progression from bladder to kidney infection require further investigation.

Pyelonephritis can also be caused by seeding of the kidneys from bacteremia. It is possible that some cases of pyelonephritis are associated with seeding of the kidneys from bacteria in the lymphatics.

MICROBIOLOGY — The microbial spectrum of uncomplicated cystitis and pyelonephritis in women consists mainly of *Escherichia coli* (75 to 95 percent), with occasional other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and other bacteria such as *Staphylococcus saprophyticus* [5,6]. Other gram-negative and gram-positive species are rarely isolated in uncomplicated UTIs. Therefore, local antimicrobial susceptibility patterns of *E. coli* in particular should be considered in empiric antimicrobial selection for uncomplicated UTIs.

Among otherwise healthy nonpregnant women, the isolation of organisms such as lactobacilli, enterococci, Group B streptococci, and coagulase-negative staphylococci other than *S. saprophyticus* from voided urine most commonly represents contamination of the urine specimen [7,8]. This is supported by a study of 202 premenopausal, nonpregnant women who presented with at least two symptoms of acute cystitis, collected a midstream, clean-catch urine, and subsequently underwent urethral catheterization to collect a bladder urine specimen [9]. There was high concordance between growth on voided and catheterized specimens for *E. coli*, even at counts as low as 10 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 <10⁴ CFU/mL, and *E. coli* was also isolated. These data suggest that enterococci and group B streptococci only rarely cause cystitis.

However, it may be appropriate to consider such organisms likely causative agents in symptomatic women when found in voided midstream urine at high counts and with pure growth.

**Antimicrobial resistance** — There is considerable geographic variability among *E. coli* for in vitro susceptibility. In four large studies, resistance rates were higher in US medical centers than in Canadian medical centers, and higher in Portugal and Spain than other European countries [10-13]. In general, resistance rates >20 percent were reported in all regions for ampicillin, and in many regions for trimethoprim (with or without sulfamethoxazole). Fluoroquinolone resistance rates were <10 percent in most parts of North America and Europe, but there was a clear trend for increasing resistance over time [10-15]. In fact, in a subsequent study of *E. coli* urinary isolates from outpatients in the United States, resistance rates to ciprofloxacin were shown to increase from 3 to 17 percent
between 2000 and 2010 among the population examined [14]. More specifically, in a population-based study of over 5000 *E. coli* urinary isolates collected in Minnesota between 2005 and 2009, the incidence of bacteriuria with isolates resistant to fluoroquinolones and/or *trimethoprim-sulfamethoxazole* increased significantly among elderly patients and those with community-associated isolates but not among nosocomial or health care-associated cases [15]. Such data suggest that to accurately predict *E. coli* resistance rates, clinicians should use antibiograms that are stratified by patient age and location of infection onset.

However, 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 [16-18].

Resistance rates for first and second generation oral cephalosporins and *amoxicillin*-clavulanic acid are regionally variable but generally <10 percent. *Nitrofurantoin*, *fosfomycin*, and pivmecillinam (not available in the United States) had good in vitro activity in all countries investigated [10-13]. These patterns suggest these three last agents are appropriate antimicrobials for empiric therapy in most regions. Ongoing monitoring of resistance is necessary for optimization of empiric therapy. (See 'Treatment' below.)

*Trimethoprim-sulfamethoxazole* is the agent for which there are the most data to guide clinical use. In studies evaluating epidemiological predictors of resistance, the use of TMP-SMX in the preceding three to six months and travel, particularly international travel, were independent risk factors for TMP-SMX resistance in women with acute uncomplicated cystitis [19-22]. In addition, clinical, in vitro, and mathematical modeling studies have suggested a 20 percent resistance prevalence as the threshold at which TMP-SMX should not be used for treatment of acute cystitis [23,24]. (See 'Cystitis' below.)

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 inpatients or those with complicated infection and may not accurately predict susceptibilities in women with uncomplicated community-acquired infection, in whom resistance rates tend to be lower [25,26].

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing strains are increasing in number, even in the setting of uncomplicated urinary tract infection [27-29].

**CLINICAL MANIFESTATIONS** — Clinical manifestations of cystitis consist of dysuria, frequency, urgency, suprapubic pain, and/or hematuria [30]. Symptoms of cystitis can be subtle in the very young and very old.

Clinical manifestations of pyelonephritis consist of the above symptoms (symptoms of cystitis may or may not be present) together with fever (>38°C), chills, flank pain, costovertebral angle tenderness, and nausea/vomiting [31]. In some cases, the presentation may mimic pelvic inflammatory disease. Rarely, patients with acute pyelonephritis present with sepsis, multiple organ system dysfunction, shock, and/or acute renal failure.

**DIAGNOSIS** — The clinical diagnosis of uncomplicated cystitis or pyelonephritis is made in a patient who has consistent signs and symptoms of urinary tract infections and is supported by laboratory evidence of pyuria and/or bacteriuria. Assessment begins with the clinical history, guided by the clinical manifestations above. Physical examination is often not necessary for diagnosis in women
with typical symptoms of cystitis, but if performed, should include assessment for fever, costovertebral angle tenderness, and abdominal examination. A pelvic examination is indicated if factors suggesting vaginitis or urethritis are present. Pregnancy testing may also be appropriate.

Laboratory diagnostic tools consist of urinalysis (either by microscopy or by dipstick) and urine culture with susceptibility data. In healthy ambulatory women, laboratory evaluation is often not necessary to make the diagnosis of uncomplicated cystitis. Urinalysis can be useful to support the diagnosis if the clinical presentation is not typical as the absence of pyuria suggests a diagnosis other than urinary tract infection. Urine culture is helpful if there is reason to suspect antimicrobial resistance. We send urine for both urinalysis and culture in women with suspected pyelonephritis.

Imaging studies are not routinely required for diagnosis of acute uncomplicated pyelonephritis but can be helpful in certain circumstances. (See "Acute complicated cystitis and pyelonephritis", section on 'Radiographic imaging'.)

Clinical suspicion — In young nonpregnant women, dysuria, frequency, urgency, suprapubic pain, or hematuria, particularly in the absence of vaginal symptoms, are highly suggestive of a urinary tract infection. The probability of cystitis is greater than 50 percent in women with any symptom of urinary tract infection and greater than 90 percent in women who have dysuria and frequency without vaginal discharge or irritation [30]. Thus, urinalysis or culture usually add little to the diagnostic armamentarium in women with typical cystitis symptoms and are often not indicated in such cases.

Acute uncomplicated pyelonephritis is suggested by fevers, chills, flank pain, costovertebral angle tenderness, and nausea or vomiting, with or without the typical symptoms of cystitis. In such cases, we send urine for both urinalysis and culture. (See 'Urinalysis' below and 'Urine culture' below.)

Older women may have a number of nonspecific urinary symptoms (such as chronic dysuria or urinary incontinence) that may confuse the diagnosis of UTI. A systematic review of studies evaluating the diagnosis of UTI among adults older than 65 years living in the community suggested that symptoms such as chronic urinary nocturia, incontinence, and general sense of lack of well-being were common and nonspecific for UTI, and should thus not routinely prompt urine studies [32]. In contrast, fever, acute dysuria (less than one week duration), new or worsening urinary urgency, new incontinence, frequency, gross hematuria, and suprapubic or costovertebral angle pain or tenderness are more discriminating symptoms among the elderly that should prompt urine studies. In addition, urine studies are warranted in a cognitively impaired patient who has persistent change in mental status and change in character of the urine that is not responsive to other interventions such as hydration.

Urinalysis — Urinalysis for evaluation of pyuria is the most valuable laboratory diagnostic test for UTI. Pyuria is present in almost all women with acute cystitis or pyelonephritis; its absence strongly suggests an alternative diagnosis [33,34] or, in a patient with pyelonephritis, the presence of an obstructing lesion [33]. Urinalysis often is not indicated in women with typical symptoms of acute uncomplicated cystitis but can be helpful in cases in which the clinical presentation is not typical.

The most accurate method for assessing pyuria is to examine an unspun voided midstream urine specimen with a hemocytometer; an abnormal result is ≥10 leukocytes/microL [33]. White blood cell casts in the urine are diagnostic of upper tract infection. The presence of hematuria is helpful since it is common in the setting of UTI but not in urethritis or vaginitis. Hematuria is not a predictor for complicated infection and does not warrant extended therapy.

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:

- Leukocyte esterase may be used to detect >10 leukocytes per high power field (sensitivity of 75 to 96 percent; specificity of 94 to 98 percent) [35].

- The nitrite test is fairly sensitive and specific for detecting ≥10(5) CFU of Enterobacteriaceae per mL of urine, though it lacks adequate sensitivity for detection of lower colony counts and of other organisms, so negative results should be interpreted with caution [35,36]. False positive nitrite tests can occur with substances that turn the urine red, such as the bladder analgesic phenazopyridine or ingestion of beets. (See "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'.)

- 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 [30]. However, results of the dipstick test provide little useful information when the history is strongly suggestive of urinary tract infection, since even negative results for both tests do not reliably rule out the infection in such cases.

**Urine culture** — The causative organisms and their antimicrobial susceptibility profiles are frequently predictable in women with uncomplicated UTI, and thus routine cultures for such infections are generally 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 if symptoms are not characteristic of UTI, if symptoms persist or recur within three months following prior antimicrobial therapy, or if an antimicrobial-resistant or complicated infection is suspected [37-40]. In addition, urine culture and antimicrobial susceptibility testing of uropathogens should be performed in all women with acute pyelonephritis.

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 10^2 CFU/mL to improve sensitivity. 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 reflects bladder growth [9].

Growth of organisms generally thought to be contaminants should be considered a likely causative agent 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'.)

**DIFFERENTIAL DIAGNOSIS** — In otherwise healthy women, both infectious and noninfectious processes can cause symptoms of dysuria, frequency, urgency, suprapubic pain, and/or hematuria [8].

- Vaginitis – In women 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 "Approach to women with symptoms of vaginitis".)

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

- Structural urethral abnormalities – Women with urethral diverticula or strictures can present with dysuria, frequency or urgency, and gross or macroscopic hematuria. Although they may have persistent sterile pyuria, bacteriuria is not present in the absence of an infection. (See "Urethral diverticulum in women").

- Painful bladder syndrome – This is a diagnosis of exclusion in women 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 "Pathogenesis, clinical features, and diagnosis of interstitial cystitis/bladder pain syndrome").

- 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").

- Nephrolithiasis – The majority of patients with symptomatic nephrolithiasis have flank pain/renal colic in addition to gross or microscopic hematuria. In the absence of infection, fever is unusual in patients with nephrolithiasis. (See "Diagnosis and acute management of suspected nephrolithiasis in adults").

TREATMENT

Cystitis

**Antibiotic selection** — Considerations in selecting an agent for treatment of acute cystitis include efficacy, risk of adverse effects, resistance rates, propensity to cause ecological adverse effects of antimicrobial therapy (such as selection of drug-resistant organisms and development of colonization or infection with multidrug-resistant organisms), cost, and drug availability [1]. None of the antimicrobials currently available clearly outweighs the others in terms of optimizing each of these factors for treatment of acute cystitis, and the optimal antimicrobial in one region may be different from that in another.

Appropriate antimicrobials for treatment of acute uncomplicated cystitis in women include [1]:

- **Nitrofurantoin** monohydrate/macrocrystals (100 mg orally twice daily for 5 days); early clinical efficacy rate with 5 to 7 day regimen 90 to 95 percent based on randomized trials [41-45] and minimal resistance and ecological adverse effects. 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 milder degrees of renal impairment, even in older women [46-49].

- **Trimethoprim-sulfamethoxazole** (TMP-SMX; one double strength tablet [160/800 mg] twice daily for 3 days); early clinical efficacy rate with 3 to 7 day regimen 86 to 100 percent based on randomized trials [41,42,50,51]. Empiric TMP-SMX should be avoided if the prevalence of resistance is known to exceed 20 percent [23,24] or if the patient has taken TMP-SMX for cystitis in the preceding 3 months [19,20], although use of TMP-SMX is acceptable if the infecting strain is known to be susceptible. In some regions trimethoprim (100 mg twice daily for three days) is used in place of TMP-SMX and is considered equivalent [37]. (See 'Antimicrobial...
These antibiotic options and suggested treatment durations for acute uncomplicated cystitis are the same for any adult woman with acute uncomplicated cystitis, regardless of age. A systematic review of studies evaluating treatment of cystitis in community-dwelling adults \( \geq 65 \) years of age concluded that the optimal regimens are the same as those recommended for younger adults and that shorter antibiotic courses (3 to 6 days) resulted in similar outcomes as longer ones (7 to 14 days) \([58]\). The choice between these agents should be individualized based on patient circumstances (allergy, tolerability, compliance), local community resistance prevalence, availability, cost, and patient and provider threshold for failure.

If there is diagnostic uncertainty regarding cystitis versus early pyelonephritis, use of nitrofurantoin, fosfomycin, and pivmecillinam should be avoided because they do not achieve adequate renal tissue levels \([1]\).

If any of these factors preclude use of the above antibiotics, oral beta-lactams (other than pivmecillinam) are appropriate options. Acceptable beta-lactam agents include amoxicillin-clavulanate, cefpodoxime, cefdinir, and cefadroxil for a duration of seven days \([51,59,60]\). A shorter course is not adequate; cefpodoxime (three-day regimen) did not meet criteria for noninferiority to ciprofloxacin (three-day regimen) for clinical cure of acute uncomplicated cystitis in a randomized trial \([61]\). Other beta-lactams, such as cephalaxin, are less well studied but may be acceptable. Ampicillin or amoxicillin should not be used for empiric treatment given poor efficacy and high prevalence of resistance to these agents \([10-13,37]\). Beta-lactams are second-line agents because they are less effective than fluoroquinolones and TMP-SMX \([37,53,60]\). However, because of concerns about the adverse effects from fluoroquinolones, the risk-benefit balance for acute cystitis favors the use of fluoroquinolones only if other agents (including beta-lactams) cannot be used.

Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) in 3-day regimens are reasonable alternative agents, though, when possible, should be reserved for important uses other than acute cystitis \([62]\). Multiple randomized trials have demonstrated that fluoroquinolones are very effective for treatment of acute cystitis \([42,56,59,60,63-67]\), although increased resistance is mitigating the usefulness of the fluoroquinolone class. In addition, in the United States, the FDA has stated that risks of systemic fluoroquinolone antibacterial drugs outweigh their benefits for uncomplicated UTI \([68]\). (See "Fluoroquinolones", section on 'Restriction of use for uncomplicated infections'.)

**Concern for resistance** — Population-based studies have documented increasing resistance of E. coli urinary isolates to fluoroquinolones and trimethoprim-sulfamethoxazole; some studies have suggested that resistance has increased in particular among elderly patients \([15]\). Strains that produce extended-spectrum beta-lactamases (ESBL) are also increasing in frequency (see
‘Antimicrobial resistance’ above). Nitrofurantoin and fosfomycin are active in vitro against ESBL producing strains [29,69,70]. 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) [53]. In the US, resistance to all oral options is still uncommon among outpatients with E. coli cystitis. In such cases, a carbapenem is the best option (eg, ertapenem once daily either IV or IM). An in vitro study demonstrated activity of a combination regimen with cefdinir and amoxicillin-clavulanate [71], but there are no published data on clinical outcomes with this combination.

Given that cystitis is associated with increasing antimicrobial resistance and has a low risk of progression to invasive disease, antimicrobial-sparing management strategies are of increasing interest (eg, antiinflammatory drugs or delayed treatment), but warrant further study [72-74]. In one trial of 241 women with acute cystitis, 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 [74]. Fewer women in the ibuprofen group received any antibiotics compared with the fosfomycin group (35 versus 100 percent), but they were more likely to receive antibiotics 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. Thus, ibuprofen cannot be recommended as an initial approach to management of symptomatic acute cystitis.

Pyelonephritis — Urine culture and susceptibility testing should be performed in patients with known or suspected pyelonephritis, and initial empiric therapy should be tailored appropriately on the basis of the infecting pathogen [1]. The approach to empiric therapy depends on the severity of illness, the prevalence of resistant pathogens in the community, and specific host factors such as allergy or intolerance history [1].

Pyelonephritis is a more serious infection than cystitis; therefore, expected efficacy of an antimicrobial agent is of greater importance than concern about ecological adverse effects (selection of drug-resistant organisms and the development of colonization or infection with multidrug-resistant organisms) [1].

Outpatient management is acceptable for patients with mild to moderate illness who can be stabilized with rehydration and antibiotics in an outpatient facility and discharged on oral antibiotics under close supervision. In an emergency department report of 44 patients with pyelonephritis, for example, a 12 hour observation period with parenteral antibiotic therapy, followed by completion of outpatient oral antibiotics, was effective management for 97 percent of patients [75]. Inpatient management is warranted in the setting of severe illness with high fever, pain, and marked debility, inability to maintain oral hydration or take oral medications, pregnancy, or concerns about patient compliance.

Outpatient — Fluoroquinolones are the only oral antimicrobials recommended for the outpatient empirical treatment of acute uncomplicated pyelonephritis [1]. Although fluoroquinolones remain highly effective for treatment of pyelonephritis when the infecting pathogen is susceptible, there is increasing resistance to this drug class even among community uropathogens [14]. Since timely use of an agent with in vitro activity is essential to treat pyelonephritis and minimize progression of infection, the threshold for selecting an antibiotic for empiric broad-spectrum therapy should be set at a relatively low resistance prevalence. For fluoroquinolones, a resistance prevalence of 10 percent has been suggested based on expert opinion [1].

Thus, for patients with mild to moderate pyelonephritis in whom the likelihood of fluoroquinolone resistance is expected to be less than 10 percent (ie, the community prevalence is not known to be higher than 10 percent, there has been no travel to an area with endemic resistance >10 percent,
and there has been no exposure to a fluoroquinolone in the last three to six months), we suggest a fluoroquinolone for empiric therapy (ciprofloxacin [500 mg orally twice daily for seven days or 1000 mg extended release once daily for seven days] or levofloxacin [750 mg orally once daily for five to seven days]) [76-80]. This can be administered with or without an initial intravenous dose of a long-acting parenteral antimicrobial (such as ceftriaxone 1 gram or a consolidated 24-hour dose of an aminoglycoside) [76,81]. In contrast, for patients with more severe pyelonephritis or risk factors for resistance, intravenous therapy with such a long-acting, broad spectrum parenteral antimicrobial should be administered until susceptibility data are available. In all cases, subsequent therapy should be tailored based on susceptibility data.

In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg [one double-strength tablet] twice-daily) or an oral beta-lactam, if the uropathogen is known to be susceptible. If either of these agents is used in the absence of susceptibility data, an initial intravenous dose of a long-acting parenteral antimicrobial should be administered (such as ceftriaxone or a consolidated 24 hour dose of an aminoglycoside). Patients unable to tolerate these agents (due to hypersensitivity and/or resistance) may be treated with aztreonam (1 g IV every 8 to 12 hours). (See "Dosing and administration of parenteral aminoglycosides", section on 'Gentamicin and tobramycin dosing in adults'.)

Subsequent therapy should be guided by susceptibility data. Appropriate options include oral ciprofloxacin, oral levofloxacin or oral trimethoprim-sulfamethoxazole [76-78]. Ciprofloxacin in a seven-day regimen or levofloxacin in a five- to seven-day regimen can be used in most patients with mild to moderate disease who have a rapid response to treatment. The duration of treatment with trimethoprim-sulfamethoxazole approved by the United States Food and Drug administration is 14 days, but clinical experience suggests that 7 to 10 days is effective in women who have a rapid response to treatment [7].

Oral beta lactam agents are less effective than other agents for treatment of pyelonephritis [37,82]. If the pathogen is susceptible and an oral beta lactam agent is continued, it should be administered for at least 10 to 14 days.

Use of nitrofurantoin, fosfomycin, and pivmecillinam should be avoided in the setting of pyelonephritis because they do not achieve adequate renal tissue levels [1].

Inpatient — Women with pyelonephritis requiring hospitalization should be treated initially with an intravenous antimicrobial regimen such as a fluoroquinolone, an aminoglycoside (with or without ampicillin), an extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem [7]. The choice between these agents should be based on local resistance data and tailored on the basis of susceptibility results.

Pyelonephritis caused by extended-spectrum beta-lactamase (ESBL)-producing strains should be treated with a carbapenem [83,84]. Empiric antibacterial coverage for ESBL-producing organisms is warranted for patients presenting with sepsis involving the urinary tract [83]. (See "Extended-spectrum beta-lactamases".)

Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antibiotic therapy. Fluoroquinolone serum levels achieved with oral and intravenous dosing are equivalent, and the modes of delivery are equally effective clinically [85]. Regimens and dosing are as outlined in the preceding section. (See 'Outpatient' above.)

The duration of antibiotic therapy need not be extended in the setting of bacteremia in the absence of other complicating factors; there is no evidence that bacteremia portends a worse prognosis [85].
Follow-up — Follow-up urine cultures are not needed in patients with acute cystitis or pyelonephritis whose symptoms resolve on antibiotics.

Patients with acute cystitis or pyelonephritis who have persistent symptoms after 48 to 72 hours of appropriate antimicrobial therapy or recurrent symptoms within a few weeks of treatment should have evaluation for complicated infection as discussed separately. Urine culture should be repeated and empiric treatment should be initiated with another antimicrobial agent. (See "Acute complicated cystitis and pyelonephritis").

Symptomatic therapy — Clinical manifestations should respond to antimicrobial therapy within 48 hours. In the interim, for some patients with cystitis a urinary analgesic such as over-the-counter oral phenazopyridine three times daily as needed may be useful to relieve discomfort due to severe dysuria. A two-day course is usually sufficient to allow time for symptomatic response to antimicrobial therapy and minimize inflammation. In fact, dysuria is usually diminished within a few hours after the start of antimicrobial therapy [86]. This agent should not be used chronically since it may mask clinical symptoms requiring clinical evaluation.

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

SUMMARY AND RECOMMENDATIONS

- Acute cystitis refers to infection of the bladder (lower urinary tract); it can occur alone or in conjunction with pyelonephritis (infection of the kidney – the upper urinary tract). Cystitis and pyelonephritis are generally considered to be uncomplicated in otherwise healthy nonpregnant adult women. Risk factors include recent sexual intercourse, recent spermicide use, and a history of urinary tract infection. (See 'Epidemiology' above.)

- The microbial spectrum of uncomplicated cystitis and pyelonephritis in women consists mainly of Escherichia coli (75 to 95 percent), with occasional other species of Enterobacteriaceae, such as Proteus mirabilis and Klebsiella pneumoniae, and other bacteria such as Staphylococcus saprophyticus. (See 'Microbiology' above.)

- Clinical manifestations of cystitis consist of dysuria, frequency, urgency, suprapubic pain and/or hematuria. Clinical manifestations of pyelonephritis consist of the above symptoms (symptoms of cystitis may or may not be present) together with fever (>38°C), chills, flank pain,
costovertebral angle tenderness, and nausea/vomiting. (See ‘Clinical manifestations’ above.)

- Laboratory diagnostic tools consist of urinalysis (either by microscopy or by dipstick) and urine culture with susceptibility data. Imaging studies are not routinely required for diagnosis of acute uncomplicated pyelonephritis but can be helpful in certain circumstances. (See ‘Diagnosis’ above.)

- For treatment of acute uncomplicated cystitis in women, we suggest nitrofurantoin (100 mg orally twice daily for five days), trimethoprim-sulfamethoxazole (TMP-SMX; one double strength tablet [160/800 mg] twice daily for three days), fosfomycin (3 grams single dose), or pivmecillinam (400 mg orally twice daily for three to seven days) (Grade 2B). TMP-SMX should be avoided if the prevalence of resistance is known to exceed 20 percent or if the patient has taken TMP-SMX in the preceding three months, although its use is acceptable if the infecting strain is known to be susceptible. The choice between these agents should be individualized based on patient circumstances (allergy, tolerability, compliance), local community resistance prevalence, availability, and cost. Beta-lactams (other than pivmecillinam) are second-line agents. Fluoroquinolones are also reasonable alternative agents, although when possible they should be reserved for important uses other than acute cystitis. (See ‘Cystitis’ above.)

- For outpatient treatment of uncomplicated pyelonephritis we suggest ciprofloxacin (500 mg orally twice daily for seven days or 1000 mg extended release once daily for seven days) or levofloxacin (750 mg orally once daily for five to seven days) (Grade 2B). The bioavailability and urinary penetration of fluoroquinolones with oral dosing is comparable to intravenous dosing. In women who have severe pyelonephritis, live in areas where the prevalence of fluoroquinolone resistance is known or suspected to exceed 10 percent, have other risk factors for fluoroquinolone resistance as described above, or cannot tolerate oral fluoroquinolone therapy, intravenous therapy with a long-acting parenteral antimicrobial such as ceftriaxone (1 gram) or an aminoglycoside (consolidated 24 hour dose) should be administered until susceptibility data are available. Subsequent therapy should be guided by susceptibility data. (See ‘Pyelonephritis’ above and "Dosing and administration of parenteral aminoglycosides", section on ‘Gentamicin and tobramycin dosing in adults’.)

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Contributor Disclosures

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