The assessment and management of urinary tract infections in adults: Guidelines for pharmacists

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Introduction

Urinary tract infection (UTI) is one of the most common indications for which antimicrobials are initiated.[1-3] UTIs cause symptoms that are often distressing for patients and can lead to serious complications. They are also often overscreened by means of obtaining urine cultures when not clinically indicated and, especially in the case of asymptomatic bacteriuria (ASB), overtreated.[3,4] In this era of increasing antimicrobial resistance, antimicrobial stewardship has become a highly important measure in the struggle to preserve the effectiveness of available antimicrobials. The Infectious Diseases Society of America (IDSA) defines antimicrobial stewardship as coordinated interventions designed to improve and measure the appropriate use of antimicrobials, with the goal of achieving best clinical outcomes while minimizing toxicity and other adverse events, thereby decreasing the selective pressure for antimicrobial-resistant strains.[5] Although antimicrobial stewardship programs and initiatives have largely been localized to hospitals and other institutions, community-based health care professionals have an important role to play in antimicrobial stewardship as well.

Pharmacists, with increasing presences in the community, hospital and ambulatory care settings, are well positioned to have important roles in the assessment and management of UTIs. In some provinces, pharmacists already have the authority to manage UTIs, to varying degrees. In New Brunswick, uncomplicated UTI is one of the conditions on the list of ambulatory conditions for which pharmacists have the authority to prescribe.[6] In Quebec, pharmacists can prescribe for UTI in females if there has been a diagnosis of UTI and a resulting prescription to treat it in the past year.[7] In Saskatchewan, prescribing for UTI in females has been proposed, but is not yet approved.[8] And in Alberta, pharmacists who have Additional Prescribing Authorization are able to prescribe for UTI if it is within their scope of practice and if, through their own assessment or collaboratively with another health professional, it is determined that treatment is appropriate.[9] Regardless of whether the pharmacist is taking responsibility for initiation of therapy for a UTI, the pharmacist can play an important role in the assessment of UTI and, when indicated, ensuring that antimicrobial treatment is appropriate. Pharmacists often receive prescriptions suggesting a diagnosis of UTI or are referred patients from other health care providers with a suspected UTI. These are valuable opportunities for the pharmacist to assess the appropriateness of treatment. In addition, the pharmacist has an important role in the education of other health care providers on the appropriate use of antimicrobials.

The purpose of this document is to serve as a guideline for pharmacists to address the assessment and management of UTI in adults in various settings.

Methods

A literature search was conducted in PubMed, Scopus and the Cochrane Library to identify

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publications relating to the treatment of UTI. Articles were limited to those published in the English language. Additional articles were identified from bibliographic reviews of relevant publications. Preference was given to guideline and review articles. From these, a guideline for pharmacists was created reflecting these best practice documents.

Results

Step 0: Know the difference between UTI and ASB

UTI is defined as a bacterial infection of the urinary tract and can involve both the lower (cystitis) and upper (pyelonephritis) urinary tract. Cystitis typically presents with symptoms such as dysuria with or without frequency, urgency, suprapubic pain or hematuria. Symptoms suggestive of pyelonephritis include fever, chills, flank pain or tenderness, with or without the typical symptoms of cystitis above.[2] Characteristics of the urine itself, such as being malodorous or smelly, or being cloudy, milky or turbid, are *not* valid indicators of UTI by themselves.[4,10,11]

ASB is the presence of bacteria in the urine without symptoms attributable to the urinary tract. Only pregnant patients and patients who will be undergoing a genitourinary procedure with mucosal breach, such as a transurethral resection of the prostate, require treatment of ASB. In other populations, ASB may be very common; but treating ASB in these populations has not been shown to improve morbidity or mortality, and some studies indicate that treatment produces more harmful effects than good.[3,10,12] Exposing patients to unnecessary antimicrobial therapy may select for and lead to subsequent infection with antimicrobial-resistant organisms (AROs), cause secondary infections (including *Clostridium difficile*) and is associated with increased risk of adverse effects and increased costs to the patient and health care system.[3,11,12]

Step 1: Assessing for UTI

If a patient presents to a pharmacist complaining of symptoms of UTI, the pharmacist should further assess to confirm the symptoms that the patient is experiencing. If a patient has been prescribed an antibiotic for a presumed UTI, the pharmacist should also assess here to confirm the appropriateness of treatment. Patients should be asked about symptoms such as dysuria, frequency, urgency, suprapubic pain, flank pain or tenderness, fever, or hematuria in non-catheterized patients. In catheterized patients, symptoms suggestive of UTI include fever, rigors, flank pain or tenderness, acute hematuria, purulent discharge from catheter site and new or worsening mental status (in the presence of leukocytosis) with no identifiable alternative cause.[13-15] If the patient has had a urinalysis or urine dipstick showing pyuria, or a urine culture with a significant amount of uropathogen(s) present, in the absence of symptoms, this would be consistent with ASB (see Step 0).

Elderly patients can be more difficult to assess for UTI for several reasons. Some may have baseline cognitive impairment that limits their ability to recall or communicate their symptoms. They may have concurrent illnesses that present with nonspecific symptoms, such as urinary incontinence, that can interfere with the ability to assess for acute symptoms.[14-16] See Table 1 for criteria for UTI diagnosis in elderly patients who have significant medical comorbidities.[14,15,17] For elderly patients with nonspecific symptoms, such as worsening mental or functional status; increased confusion, delirium or agitation; or new or more frequent falls, if their medical status is not rapidly declining and they are not on a fluid restriction, it is preferable to hold antibiotics, ensure adequate hydration and observe. Often this will be sufficient for symptoms to resolve. If typical UTI symptoms develop, then treatment as for a UTI is warranted. If nonspecific symptoms continue without the development of typical symptoms, assessing for other causes of the nonspecific symptoms, such as recent medication changes, uncontrolled pain, dehydration, hypoxia or other alternate causes, should be undertaken. If nonspecific symptoms resolve without the development of typical symptoms, no further intervention is necessary.[4,14,17]

In women with dysuria, if there is also vaginal discharge or odour, pruritis, painful intercourse, and no urinary frequency or urgency, vaginitis becomes more likely than UTI.[18]

Step 2: Assess for presence of complicating factors

Once it has been determined that the patient has symptoms consistent with UTI, evaluation for complicating factors is essential. UTIs are considered complicated when they are associated with structural, functional or metabolic conditions that promote UTI. These patients have an

TABLE 1 Criteria for symptomatic UTI in elderly patients with comorbidities

Noncatheterized	Catheterized

Minimum criteria include 1 of the following:
• Acute dysuria or acute pain, swelling or tenderness of testes, epididymis or prostate
OR
• Fever (≥38°C or increase of at least 1.1°C above baseline), rigors or leukocytosis and at least 1 of the following symptoms (see below)
OR
• At least 2 of the following *symptoms*:
  • New or increased frequency
  • New or increased urgency
  • New or increased incontinence
  • Suprapubic pain
  • Acute flank pain or tenderness
  • Gross hematuria
	Minimum criteria include *no alternative diagnosis* AND 1 of the following:
	• Fever (≥38°C or 1.1°C above baseline), rigors or new-onset hypotension
	• Leukocytosis and either an *acute change* in mental status or acute functional decline
	• New-onset flank or suprapubic pain or tenderness
	• Purulent discharge from catheter site
	• Acute pain, swelling or tenderness of testes, epididymis or prostate

increased likelihood of resistant pathogens and may be more likely to experience treatment failure.[2,11] Examples of complicating factors include UTIs in males, chronic obstruction, nephrolithiasis, poorly controlled diabetes, indwelling urinary catheter, chronic renal insufficiency, pregnancy and immunosuppression (see Box 1 for examples of complicating factors).

Instances where patients should be referred for physician assessment include likely upper UTI (pyelonephritis), patients who appear systemically unwell or septic, suspicion of obstruction requiring urologic investigation, patients with a history of recurrent UTI and an increase in the frequency or severity of symptoms, pregnancy, recent urologic intervention or surgery, or if other aspects of the patient's presentation are felt to be beyond the ability of the individual pharmacist to assess. Isolated epididymitis/orchitis should be assessed by a physician to rule out other conditions, such as sexually transmitted infection. Isolated testicular pain and swelling should also be assessed by a physician to exclude torsion, which is a medical emergency.

Step 3: Considerations for laboratory assessment

If the patient does not have symptoms indicative of UTI, sending a urine culture is not recommended. If a culture is performed on an asymptomatic patient and results in the presence of bacteria that is not attributable to contamination, this is consistent with ASB. Screening for and treatment of ASB is not recommended, unless the patient is pregnant or going to be undergoing an invasive genitourinary procedure, as outlined above.[3,12] However, some clinicians have difficulty ignoring a positive urine culture, even when the patient is asymptomatic. One study of hospitalized patients showed that by not routinely reporting urine culture results in noncatheterized patients, the rates of inappropriate treatment of ASB were reduced from 48% to 12%.[20] Therefore, one should avoid sending a urine culture in the absence of symptoms to limit the pressure to treat (should the culture result be positive).

If the patient has an uncomplicated UTI, sending a urine culture is usually not necessary. *Escherichia coli* is the most likely pathogen,

BOX 1 Examples of complicating factors[2,11,19]

- Male sex
- Chronic obstruction
- Nephrolithiasis
- Poorly controlled diabetes
- Indwelling urinary catheter
- Indwelling urinary stent or nephrostomy tube
- Chronic renal insufficiency
- Pregnancy
- Immunosuppression (e.g., chronic high-dose corticosteroid use, use of other immunosuppressives, neutropenia, etc.)

causing up to 95% of uncomplicated UTIs.[1,2] The reliability of the clinical diagnosis, coupled with the limited interpretability of quantitative urine cultures in uncomplicated UTI and the predictable microbiology, makes empiric treatment without a culture reasonable.[2,21] Also, studies of placebo for uncomplicated UTI have shown that clinical cure can occur in up to 42% of women who are either untreated or are treated with an agent that does not possess *in vitro* activity against the isolated pathogen.[1,22] Instances in which a urine culture is more strongly indicated in uncomplicated UTI include if there is early recurrence of infection, if presentation is atypical, or when pyelonephritis is a consideration.[21]

In cases of complicated UTI or pyelonephritis, a urine culture should always be sent. This is due to the broader range of pathogens that are likely to be causative and the higher likelihood of these pathogens being more resistant.[11,19] If the patient has a urinary catheter that has been in place for 2 weeks or longer, it should be discontinued or changed before collection of the specimen.[4,13] The reason for this is that when catheters have been in place for this amount of time, there is a very high likelihood of bacterial biofilm production. Biofilms are problematic in that urine cultures taken from these catheters may reflect the bacteria in the biofilm and not what is actually in the bladder, as well as the fact that these biofilms protect uropathogens from antimicrobials. In addition, urinary catheters that have been in place for this amount of time will virtually always result in a positive culture—in the absence of symptoms, this would be consistent with ASB.

Pharmacists who are unable to order urine cultures should advocate for or make recommendations to have them done when they are appropriate and should discourage the sending of urine cultures when they are not indicated.

Pyuria (leukocytes in the urine) identified by urinalysis or urine dipstick does not identify symptomatic infection, as it is also present in the majority of patients with ASB. It does, however, provide a high negative predictive value; therefore, the absence of pyuria may be used to exclude symptomatic infection.[11,13] This negative predictive value is higher in elderly patients than in younger patients with symptoms strongly suggestive of acute uncomplicated UTI.[2,14,21] Therefore, for uncomplicated UTI in younger patients, a urinalysis or urine dipstick should not be obtained, and patients should be treated on the basis of the presence of symptoms alone. For elderly patients, in the absence of pyuria, urine culture or treatment should not be pursued. In pregnant women, screening for pyuria alone should not be done, as a high proportion of patients will be negative for pyuria but still have ASB.[10]

Blood cultures should be considered if the patient is febrile, hemodynamically unstable, if pyelonephritis is suspected or if the patient is immunocompromised.[21,23]

Step 4: Considerations for treatment

If a urine culture is to be sent, the specimen should be collected before the initiation of antibiotics. While the results of the urine culture are pending, the initiation of antibiotics should be delayed until the results of the culture are available, if possible. This way, therapy can be directed at the specific pathogen(s).[2,11] When antibiotics are started empirically, the choice of agent should be reevaluated once culture results are available.

In the case of uncomplicated UTI, the IDSA stresses the importance of considering "collateral damage" when selecting antimicrobial agents, that is, the ecological adverse effects, such as selection of AROs.[1] They propose that the preserved *in vitro* susceptibility of *E. coli* to nitrofurantoin and fosfomycin over the years may suggest that these agents cause only minor collateral damage, possibly because of negligible effects on fecal flora. Agents such as the fluoroquinolones are known to affect fecal flora to a larger extent and have been associated with increased rates of antimicrobial resistance and *C. difficile* infection. This, coupled with the high rate of spontaneous resolution of symptoms in uncomplicated UTI, makes keeping collateral damage to a minimum by avoiding agents such as fluoroquinolones desirable and achievable. Also, the Food and Drug Administration recently issued a warning stating that the risk of serious side effects of fluoroquinolones outweighs the benefits in uncomplicated UTI and that they should be avoided for this indication.[24] Therefore, fluoroquinolones should not be used as first-line agents in uncomplicated UTI.[1] See Table 2 for suggested empiric first-line agents.[1,11,23,25] Pharmacists should also familiarize themselves with the local antibiogram, as this will assist in the selection of empiric therapy. They should keep in mind, however, that resistance rates portrayed in hospital antibiograms may not be representative of the expected resistance patterns of

TABLE 2 Recommended first-line empiric treatment of urinary tract infection

Uncomplicated*	Complicated, nonsevere	Severe/septic/pyelonephritis†
• Nitrofurantoin PO × 5 days • TMP/SMX PO × 3 days • TMP PO × 3 days • Fosfomycin tromethamine PO × 1 dose	• Cefixime PO × 7-10 days • Amoxicillin-clavulanate PO × 7-10 days • TMP/SMX PO × 7-10 days • Fluoroquinolones‡ PO × 7-10 days	• Ceftriaxone IV ± ampicillin IV • Gentamicin IV ± ampicillin IV If clinically appropriate, may step down to PO therapy to complete 7-14 day course

PO, orally; TMP, trimethoprim; SMX, sulfamethoxazole; IV, intravenously.
*Longer durations should be considered if relapse (recurrent infection within 4 weeks of treatment completion).
†The decision of which antibiotic to use should always be based on knowledge of local antimicrobial resistance of *Escherichia coli* or other gram-negative organisms
‡Resistance to fluoroquinolones is increasing and has reached unacceptable levels in some regions. Fluoroquinolones should be considered alternatives, rather than first-line, in areas where resistance is high.

uncomplicated infections, as these antibiograms are often heavily influenced by patients with complicated and nosocomial infections, which tend to be more resistant in nature.[1,2] Because of increasing fluoroquinolone resistance[26] and the need to reserve these agents for more severe infections, fluoroquinolones should also be considered as alternatives for complicated infections and not first-line therapy, in areas where there is a high rate of resistance to them (i.e., resistance of *E. coli* exceeding 10%). Nitrofurantoin and fosfomycin are not indicated for upper UTI.[1,11]

Additional considerations that should factor into the treatment decision include patient allergies, recent antibiotic exposure, recent prior urine culture results, drug interactions, contraindications, cost and other patient factors, such as renal status.

Pharmacists who are able to perform therapeutic substitutions may choose to do so, if appropriate, to optimize antimicrobial therapy based on their assessment and/or once culture results are available. Pharmacists who are not able to do this should advocate for changes, when indicated.

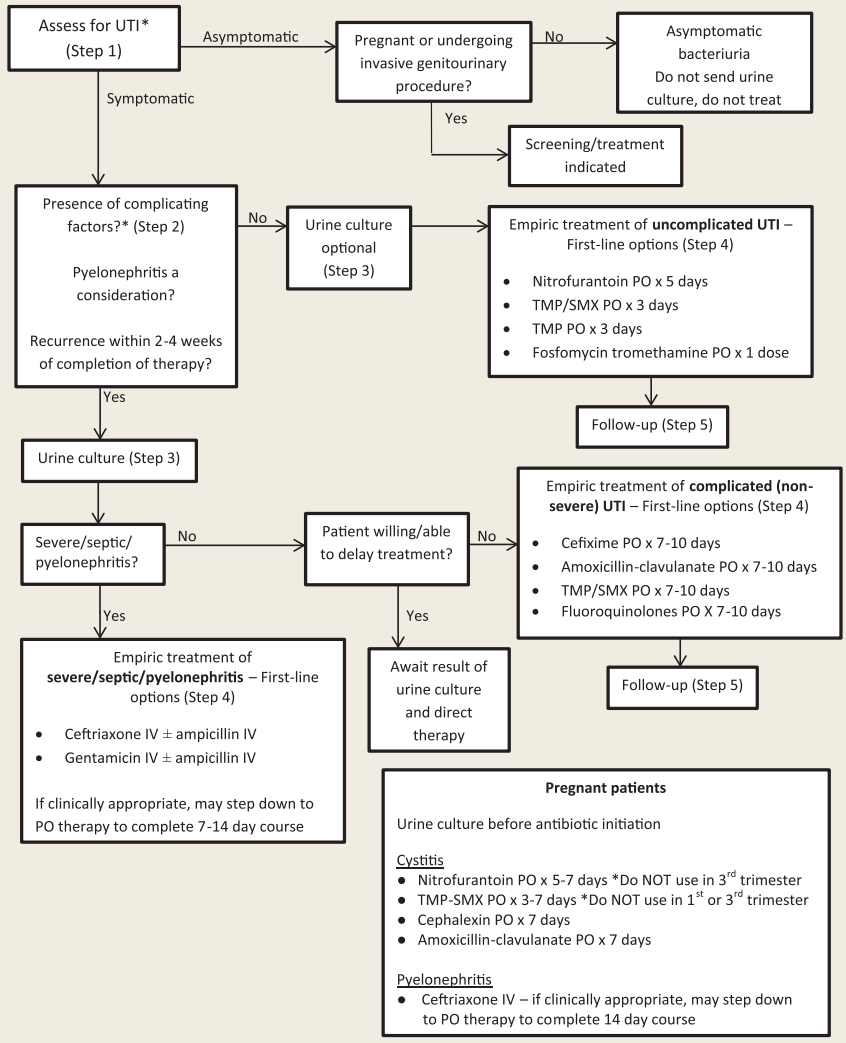
Step 5: Follow-up

If a urine culture was sent, these results need to be followed up. Most urine cultures have a turnaround time of about 24 to 72 hours. If antimicrobial therapy was delayed in symptomatic patients, the results of the urine culture should direct therapy. If therapy was started empirically, the urine culture results should be checked to ensure that the regimen covers the offending pathogen and then adjust, including narrowing the spectrum to minimize collateral damage, if appropriate.[1,11,23] Pharmacists who have access to electronic health records should easily be able to follow up on these results. Others may need to be more creative, such as having the results faxed to them.

Patients can usually expect to have improvement in symptoms within 48 to 72 hours of treatment[2,11,21]; therefore, changing agents due to lack of response before this time should be avoided (unless urine cultures suggest the need for a change). If there has been no improvement in the patient's symptoms beyond this time, the patient should be reevaluated for missing antimicrobial coverage, alternate sources of infection and other factors, such as poor adherence to therapy. Patients with complicated UTI who do not respond in this time and in whom the lack of response is not attributable to the aforementioned factors should be assessed promptly by a physician to exclude urinary obstruction, abscess or other abnormalities that may require source control.[11] Red flag symptoms, including fever, rigors, flank pain and significant nausea/vomiting, should be evaluated at all follow-up encounters and prompt emergency medical assessment, if present.

Patients who have early recurrence of infection after completion of therapy should have a urine culture sent. Recurrence within 1 month of completion of therapy is usually considered a relapse, for which the same organism is the most likely cause. Relapse may require urologic investigation, depending on the individual case. If the culture shows a resistant pathogen, then treatment with an appropriate antimicrobial would be indicated. If the organism is not resistant to the previously used antimicrobial, then referral to a physician to identify a reason for recurrence would be warranted, as ongoing culture of the same organism raises the possibility

FIGURE 1 Proposed algorithm for assessment and management of urinary tract infection



*See text for assessment considerations.

of a complicating factor that requires investigation (i.e., prostatitis, infected stone, abscess). Recurrence after 1 month of completion of therapy is usually a reinfection, which is due to a different organism or strain than the original infection. Reinfection in patients with uncomplicated UTI usually does not require urologic investigation.[2,21,23]

Sending a urine culture following completion of antibiotics is not necessary if symptoms have resolved.[2,21,23] Doing so may create pressure for the treatment of ASB, if bacteria turn up in the urine of a patient who no longer has symptoms. An exception to this is pregnant patients, for whom ongoing screening and treatment of ASB is recommended, as untreated ASB in this population is associated with higher rates of pyelonephritis and adverse fetal outcomes.[2,23]

Discussion

This document is intended to act as a general guideline for pharmacists to enhance their ability to appropriately assess and manage UTI. To our knowledge, there are no existing guidelines intended specifically for pharmacists for the assessment and management of UTI. This guideline is applicable to primary care pharmacists in various practice settings, such as community and ambulatory care settings, as well as to hospital practice. It can be used by a pharmacist assessing and managing a UTI themselves or by a pharmacist entering a patient's care after

an assessment has already been performed by another health care provider. It could also be used by a pharmacist after initial assessment and treatment have already been initiated by another health care provider.

There are several important areas of UTI management that are beyond the scope of this document. The management of UTI in pregnancy is not covered here in great detail, as this is an area that is typically managed during prenatal care. Other areas beyond the scope of this document include long-term prophylaxis of UTI, acute or chronic prostatitis and UTI in pediatric patients. Interpretation of microbiologic colony counts is not included in this document, as many microbiology labs typically report the significance of the counts with their reports. Also, in the empiric treatment recommendations, specific doses/dosing intervals are not provided, just the agents and durations. This is to leave it open to the pharmacist to select the appropriate regimen based on patient-specific factors. This guide is not intended to replace clinical judgment.

To our knowledge, there are no published studies on the impact of the management of UTI by pharmacists other than studies of the effect of educational interventions. This could be a good area for future pharmacy practice research. We look forward to the results of the R_xOUTMAP study (Outcomes of Urinary Tract Infection Management by Pharmacists), a trial of pharmacist prescribing and care of uncomplicated UTI in New Brunswick (ClinicalTrials.gov - NCT03184818), scheduled for completion in early 2018. ■

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