Diagnosis and management of simple and complicated urinary tract infections (UTIs)

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Urinary tract infections (UTIs) remain a common clinical problem in both the community and healthcare-associated settings. Each patient should be carefully assessed to ensure that a correct diagnosis is made and that antimicrobial therapy is appropriately prescribed—defined as using a clinically indicated agent in the correct dose and route of administration, for the correct duration—for symptomatic patients, and avoided for most asymptomatic patients. This should help stem the growing tide of antimicrobial resistance and allow for the continued use of simpler, less expensive agents. Continued surveillance and monitoring of antimicrobial resistance rates will be critical to help formulate and update future treatment recommendations for all categories of patients with UTIs.

Key Words: UTI, antimicrobial resistance, ESBL

Introduction

Urinary tract infections (UTIs)—bacteriuria and true symptomatic infections—remain one of the most common reasons patients in the community seek medical attention and are prescribed an antibiotic. Most patients in outpatient settings who have UTIs are premenopausal women, and in some studies, as many as 50% of women have reported having at least one UTI by age 30.[1,2] The recurrence rate is high, and a study reported that about 25% of women experienced a second episode within 6 months of their first UTI.[3] In the hospital setting, UTIs remain the most common healthcare-associated infections worldwide, and this reflects the widespread, often inappropriate use of urinary catheterization.[4] Thus the impact of UTIs in terms of cost and healthcare resources is considerable, and it is important to have a rational approach to managing, treating, and preventing them.[3]

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Diagnosis

The initial approach to manage UTIs requires a careful assessment of the patient in order to stratify them into one of three categories of UTIs: asymptomatic bacteriuria; uncomplicated (simple) UTI; or complicated UTI. Further classification may be made to determine if patients have recurrent UTIs due to reinfection or relapse. The initial separation of patients into having one of these three categories of UTIs will impact the extent of the work up that is performed, the location of treatment (i.e., outpatient versus inpatient), and the selection and duration of antimicrobial therapy.

Asymptomatic bacteruria

Asymptomatic bacteriuria refers to the presence of a significant amount of bacteria in a urine specimen that was collected from a patient with no symptoms, and which was sent for a laboratory urine culture test.[5] Most often, the reason the specimen was submitted for urine culture is unclear. Asymptomatic bacteriuria is common, and 3% to 8% of premenopausal women and 4% to 43% of postmenopausal women may have this condition.[5] In most cases, treatment is not indicated, since there is no evidence that patients would derive any benefit from it.[5]

Uncomplicated UTIs

Although the distinction between uncomplicated and complicated UTIs is not always clear, this distinction does aid in making clinical decisions regarding patient treatment and management.[6] Uncomplicated UTIs are generally defined as those occurring in otherwise healthy premenopausal women who have kidneys and urinary tract systems with normal function. Uncomplicated UTIs include infections in both the lower urinary tract (cystitis) as well as the upper urinary tract (pyelonephritis).[7] Patient symptoms may have an acute or recent onset and may include urinary frequency, pain/burning on urination, urgency, foul smelling/cloudy urine, other features of dysuria, as well as features suggestive of an upper urinary tract infection (pyelonephritis) such as flank pain and fever.

Complicated UTIs

Several factors, as listed in Table 1, may make a UTI complicated. Complicated UTIs usually develop in patients with urinary tract systems that are structurally or functionally abnormal due to intrinsic or extrinsic factors.

Treatment strategies

Asymptomatic bacteruria

Among women with asymptomatic bacteruria, those who are pregnant or who are undergoing a genitourinary procedure may require further investigations or treatment (as discussed later). Otherwise, most women with asymptomatic bacteriuria—including elderly women, or those with underlying diabetes, indwelling urinary-tract catheters, or spinal-cord injuries—do not require further investigations or treatment.[5,8] These patients should be reassured that no harm will come to them from not treating the bacteriuria and that a routine urine culture test is not warranted. Similarly, there is also no data to support the screening and/or treatment for asymptomatic bacteriuria in men.[5]

TABLE 1. **Underlying factors associated with complicated urinary tract infections**

- Anatomical or functional abnormality of the urinary tract system
- Renal insufficiency
- Presence of foreign body
- Transplantation
- Comorbid illness
- Antimicrobial-resistant organism(s)
- Recent antibiotic use*
- Elderly
- Male
- Recurrent urinary tract infection
- Pregnancy
- Recent urologic procedure or manipulation of the genitourinary tract system
- Symptoms > 14 days
- Immunocompromised host

*Within 3 months of the UTI, regardless of which antibiotic the patient received and for what reason

The most important group for whom screening and treatment of asymptomatic bacteriuria has been shown to be beneficial is pregnant women.[5] It is recommended that all pregnant women should provide a urine specimen for culture to screen for asymptomatic bacteriuria during their routine visit to a physician for prenatal care in their first trimester. If significant bacteria is detected, these women should receive appropriate antibiotic therapy and then a follow up urine specimen should be submitted for a urine culture test to ensure that the organism has been eliminated. Untreated, asymptomatic bacteriuria in pregnant women has been associated with an increased risk of pyelonephritis in the mother and an increased risk of delivering babies who are small for their gestational age.[9] A second group of patients who may benefit from screening and treatment for asymptomatic bacteriuria are those undergoing selected manipulation of their genitourinary tract systems.[10] A urine specimen should be submitted before and after the procedure to ensure that no significant amount of bacteria is present in the bladder.

Uncomplicated UTIs

Several studies have evaluated a variety of approaches for diagnosing and managing women with suspected

uncomplicated cystitis. Little et al compared three treatment strategies—empiric treatment without urine culture; targeted treatment based on results of a urine culture; and the use of UTI symptom scores to make treatment decisions—and found no significant differences in time to symptom improvement.[11] However, although empiric treatment was as effective as the other two approaches, the study did not consider the cost of overutilization of antibiotics (that would be incurred by treating all patients presenting with symptoms suggestive of a UTI) or the potential for selective pressure for antibiotic-resistant bacteria. One study estimates that empiric treatment of women with acute cystitis might result in up to 40% of women with urinary symptoms receiving unnecessary antibiotics, since they would have had negative urine cultures.[12]

A validated clinical decision aid to determine whether a patient needs to be treated with antibiotics for an uncomplicated UTI has been developed for use in the setting of a community-based family practice. The decision aid is based on the presence of three criteria: symptoms suggestive of a UTI (especially burning or pain on urination); urine leukocytes (detected by a dipstick test based on leukocyte esterase; any amount more than trace); and urine nitrites (detected by a dipstick test that is a marker for bacteria; any amount including trace).[13] Patients are assigned one point for each criterion. Patients with one point should provide a urine specimen for a culture before any antibiotic treatment is initiated, since the likelihood of a positive result is relatively low (between 26% and 38%). Only patients with a positive urine culture for a known uropathogen should receive treatment. For patients with two or more points, empiric therapy targeting *Escherichia coli* (*E. coli*) should be prescribed without waiting for the results of a urine culture, because of the high likelihood of infection (> 70% likelihood of a positive urine culture). The use of such a clinical decision aid should help reduce the overuse of antibiotics and thus alleviate some of the selection pressure for antimicrobial resistance in the community.

Complicated UTIs

The extent of the work up and investigations required for patients with uncomplicated pyelonephritis and complicated UTIs depends on which underlying factors associated with complicated urinary tract infections (listed in Table 1) are suspected or known to exist at the time of clinical presentation. All patients with a suspected uncomplicated pyelonephritis or complicated UTI should provide a urine specimen for culture and antibiotic susceptibility testing.[7,14] As discussed later, the predictability of the likely pathogen(s) is less clear than in uncomplicated cystitis, and the likelihood of detecting an antibiotic-resistant organism is increased. Additional work up—such as abdominal ultrasound or other imaging studies, or referral to an infectious diseases specialist and/or urologist—should be determined on a case-by-case basis. These patients should receive empiric antibiotic therapy pending the results of a urine culture, based on consideration of local antimicrobial resistance rates in addition to the patient's recent antimicrobial use.

Recurrent UTIs

Determining whether a patient has a recurrent UTI will also impact patient management. Reinfection, which is the most common type of recurrent UTI, occurs more than 2 weeks after a patient has completed antimicrobial therapy and is generally due to infection with a different organism (including a different *E. coli* strain). Relapse occurs in 5% to 10% of women within 2 weeks of completing antimicrobial therapy and is caused by persistence of the same pathogen in the urinary tract system, which suggests infection with an antimicrobial-resistant pathogen.[15] Studies suggest that women who have a recurrent UTI due to reinfection should be treated with the same agent that they received for their original UTI episode; however, an alternative agent should be used if the re-infection occurs within 6 months, especially if the original agent was trimethoprim-sulfamethoxazole (TMP-SMX), due to the high risk of developing microbial resistance to TMP-SMX.[16,17] Patients with relapse may require additional assessment and investigations to determine why they did not respond to their initial therapy, and treatment should be based on the results of their urine culture.

Etiology

Most uncomplicated UTIs are due to a single bacterial pathogen, with *E. coli* isolated in 75% to 95% of cases.[7] Another 5% to 15% of cases may be due to the gram-positive organism *Staphylococcus saprophyticus* (which is almost exclusively associated with uncomplicated cystitis and not pyelonephritis), while the remaining cases are usually due to other enteric gram-negative bacteria such as *Klebsiella* species, *Proteus* species, and others. The etiology of complicated UTIs is usually more varied and is less predictable than uncomplicated UTIs. As well, the possibility of mixed infections with two or more organisms may occur. Although *E. coli* remains the most common pathogen isolated in complicated UTIs, it is found in only 50% of cases. Other, generally more resistant organisms such as *Proteus* species, *Klebsiella* species, enterococci, *Pseudomonas aeruginosa*, and even yeast may be isolated.[18]

Antimicrobial susceptibility and resistance

As with many other infectious diseases, antibiotic-resistant pathogens have become more prevalent as a cause of UTIs in both outpatient and inpatient settings.[18-20] However, the prevalence of reported antimicrobial resistance varies widely depending on the patient population, geographic location, hospital, patient ward/unit, patients' prior antibiotic use, and other factors.[19-22] Some studies of antimicrobial resistance have included men and children.[21] Others have looked at outpatient populations.[23] Yet others have used test results from routine urine specimens submitted for culture without information about age, sex, type of infection, or prior antibiotic exposure.[24,25] Given that a large proportion of patients are treated empirically without results from a urine culture, data based on routine urine specimens submitted for culture in the clinical setting may not accurately reflect the true incidence of antibiotic-resistant organisms associated with UTIs.[14,26,27] However, despite the limitations of currently available data, knowledge of local antimicrobial susceptibility and resistance rates for common uropathogens should always be considered when making treatment decisions.

In Canada, resistance of *E. coli* to TMP-SMX has been estimated to be as low as 10.8%[28] and as high as 18.9% for the same time period.[23] More recently, a study of Canadian tertiary care centers, which included both males and females as well as inpatients and outpatients, reported that 22.1% of *E. coli* infections were resistant to TMP-SMX.[25]

A higher rate of ciprofloxacin-resistant *E. coli* has been reported in British Columbia.[29] In addition, a 2010 report from the British Columbia Centre for Disease Control found that between 1998 and 2010, ciprofloxacin-resistant *E. coli* increased 10-fold.[30] However, these estimates were based on routine urine specimens submitted for culture, without clinical information regarding the patient's sex or age, or the clinical reason for obtaining the specimen.

Nitrofurantoin- resistance rates remain low in isolates of *E. coli* from women with acute cystitis in Canada.[28,29] However, resistance to this agent may be increasing in organisms other than *E. coli*.[18,25]

A growing concern has been the emergence of extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria including *E. coli* and *Klebsiella* species that are multidrug resistant. These organisms tend to be resistant not only to all generations of cephalosporins but also to the fluoroquinolones and beta-lactam/beta-lactamase inhibitor combinations (e.g., piperacillin/tazobactam), possibly leaving the carbapenems as the only current alternatives for therapy of all UTIs. A recent cross-Canada study found that most ESBL cases were from UTIs in the community, but it was not clear whether these were isolated only from women with uncomplicated cystitis or also from other patients with UTIs.[31] An international study of urinary tract isolates of *E. coli* from inpatients found that 17.9% were ESBL positive.[20] This study included both males and females, ranging from newborns to patients older than 65 years. Susceptibility to other agents in the ESBL-positive *E. coli* isolates was ≥ 98% for the carbapenems (imipenem and ertapenem), 87.1% for amikacin, 84.4% for piperacillin-tazobactam, and only 15.3% for ciprofloxacin. As knowledge of the epidemiology of ESBL-producing organisms in community and hospital settings continues to evolve, treatment choices will be significantly impacted, including treatments for women with acute cystitis.[32,33]

Antimicrobial treatment

Uncomplicated UTIs

Recent guidelines published by the Infectious Diseases Society of America (IDSA) and endorsed by Canadian and European organizations,[14] recommend that twice-daily, double-strength TMP-SMX for 3 days remains the empiric drug and dosage of choice for first-line treatment of uncomplicated cystitis in premenopausal women, unless the prevalence of TMP-SMX-resistant *E. coli* in a given region or setting exceeds 20%.[7,14] The presence of a resistant organism in a patient with acute cystitis has been associated with lower rates of microbiologic cure,[34] longer time to symptom resolution,[35] and higher rates of repeat consultations.[36] Although the prevalence of TMP-SMX-resistant *E. coli* causing acute cystitis in women in Canada remains below 20% nationally, it may exceed this level in premenopausal women depending on geographical location and prior antimicrobial exposure. These observations suggest that TMP-SMX may no longer have a role as a first-line, empirical antibiotic treatment for acute cystitis in premenopausal women in Canada as recommended by the IDSA guideline.[14]

Alternatives to TMP-SMX in the outpatient setting include nitrofurantoin twice daily for 5 days; amoxicillin-clavulanic acid; a cephalosporin (e.g., cefdinir, cefixime, etc.) for 5 to 7 days; or single-dose fosfomycin. Although the fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) given for 3 days are effective, their use should be limited in acute, uncomplicated cystitis. As with other agents, their overuse is associated with increasing antimicrobial resistance, and this may limit their use not only for UTIs but also for a variety of other indications.

Neither amoxicillin or ampicillin is recommended as an empiric treatment for uncomplicated cystitis, due to the relatively poor efficacy and the high rates of resistance to these agents. However, because of their relative safety, these agents continue to play a role in the management of pregnant women with UTIs.

It is important to recognize that the IDSA treatment recommendations are limited to premenopausal women without comorbidities such as diabetes or urological abnormalities, and therefore they cannot be directly applied to all patient populations in the outpatient setting including the elderly.[14]

Because most therapy for uncomplicated cystitis is administered empirically, an assessment of potential risk factors for antimicrobial resistance is needed prior to prescribing a treatment agent. The most important identified epidemiologic risk factor is exposure to the antibiotic in the previous 3 to 6 months. This was found to be an independent risk factor for TMP-SMX resistance in women with acute, uncomplicated cystitis.[14,16,37,38] Prior exposure to other agents has been less well studied, but reports suggest that the same phenomenon may occur, and thus consideration should be given to using an agent other than one that has been recently prescribed.[39]

For patients with acute, uncomplicated pyelonephritis, including those with severe infection and bacteremia, a recent study found that a 7-day course of ciprofloxacin was not inferior to a 14-day course of therapy.[40] Although limiting patient exposure to antibiotics and thus possibly reducing antimicrobial selection pressure for resistant organisms is desirable, the results of this study cannot be extrapolated to other agents, and thus 10 to 14 days of treatment should be prescribed when using non-fluoroquinolone agents for treatment of uncomplicated pyelonephritis. The relatively high rates of fluoroquinolone resistance in some regions/settings including ESBL-producing organisms may limit this short-course treatment in these situations. Oral ciprofloxacin for 7 days can be used for patients who do not require hospitalization, if the prevalence of resistance of community uropathogens to fluoroquinolones does not exceed 10%.[14] If the pathogen is known to be susceptible, then oral TMP-SMX twice daily for 14 days may be used. Alternatives include a third-generation cephalosporin or once-daily aminoglycoside. For women with pyelonephritis requiring hospitalization for treatment, initial therapy should be given parenterally with either a fluoroquinolone, a third-generation cephalosporin, an aminoglycoside plus/minus ampicillin, or a carbapenem. Treatment should be tailored once an organism is identified and antimicrobial susceptibility results are available.

Complicated UTIs

Treatment recommendations for patients with complicated UTIs are much less well defined. This likely reflects the varied types of patient populations who have this type of UTI. The choice of empiric antimicrobial therapy will depend on an assessment of multiple factors including antimicrobial resistance rates, presence of comorbid conditions (including assessment of renal function), drug interactions, ability of the patient to take oral antibiotics, and history of drug allergies. Initial empiric parenteral therapy with a fluoroquinolone, a carbapenem (e.g., ertapenem, meropenem, or imipenem), a third-generation cephalosporin (e.g., ceftriaxone, cefotaxime, etc.), or a piperacillin/tazobactam may be required.[41] Resistance to TMP/SMX is frequently seen in most cases of complicated UTIs, and it is not recommended for empiric therapy in these cases. As noted earlier, for patients with uncomplicated cystitis and pyelonephritis, ESBL-producing organisms also appear to be increasing in the hospital setting, rendering many of the agents listed above ineffective except for the carbapenems. The recommended treatment duration for patients with complicated cystitis is 7 to 10 days (3-day, short-course therapy is not recommended), and the recommended treatment duration for complicated pyelonephritis is 10 to 14 days.[42]

Prophylaxis

The use of antimicrobial agents as prophylaxis for recurrent cystitis has been shown to be effective in reducing the risk of recurrences by close to 95%.[43,44] Concern, however, stems from the risk of continued exposure to antimicrobial agents and the potential emergence of resistance. Current recommendations are to limit the use of antimicrobial agents for prophylaxis of UTIs to women with three or more infections in the past 12 months, or those with two or more infections in the past 6 months in which at least one episode was documented by a positive urine culture.[7] The optimal duration of antimicrobial prophylaxis is not known, but continued evaluation of the patient should be performed with consideration to discontinue it after 3 to 6 months. Approximately 50% of women will experience a UTI within 3 months of discontinuation of prophylaxis, at which point re-institution of prophylaxis should be considered.[44] At present, there is no evidence to support the use of antimicrobial prophylaxis for routine prevention of catheter-associated UTIs, and thus it should not be used for this purpose.[4]

Multiple non-pharmacologic strategies have been tried for the prevention of recurrent UTIs, despite the fact that data supporting many of these approaches

is lacking.[7] One preventative strategy that has been greatly debated has been the effectiveness of cranberry-containing products for the prevention of UTIs. A recent systematic review and meta-analysis of randomized controlled trials of cranberry-containing products concluded that their use is associated with a protective effect—the risk ratio for cranberry users versus nonusers was 0.62 (95% confidence interval [CI], 0.49 to 0.80).[45] The investigators cautioned that the results should be interpreted in the context of substantial heterogeneity across trials. The use of cranberry-containing products provides an alternative (or addition) to the use of low-dose antimicrobial prophylaxis for women with recurrent UTIs.

Summary

UTIs remain a common clinical problem in both the community and healthcare-associated settings. Each patient should be carefully assessed to ensure that a correct diagnosis is made and that antimicrobial therapy is appropriately prescribed—defined as using a clinically indicated agent in the correct dose and route of administration, for the correct duration—for symptomatic patients, and avoided for most asymptomatic patients. This should help stem the growing tide of antimicrobial resistance and allow for the continued use of simpler, less expensive agents. Continued surveillance and monitoring of antimicrobial resistance rates will be critical to help formulate and update future treatment recommendations for all categories of patients with UTIs.

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