Short-term therapy for urinary tract infection: success and failure
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Abstract
The pharmacokinetic characteristics of some antimicrobials lead to very high urinary concentrations. This, together with the superficial nature of bladder infection and effective voiding, supports the use of short-course antimicrobial therapy for treatment of acute uncomplicated cystitis. Even a single dose is effective for >90% of episodes for some antimicrobials. Short-course therapy for 3 days is, however, the current accepted standard of therapy for acute uncomplicated urinary tract infection (UTI). Complicated UTI is a more diverse clinical entity. For individuals with some underlying abnormalities, including incomplete drainage of urine or renal failure, short-course therapy is never appropriate. However, some individuals with complicated UTI have adequate urinary emptying, infection limited to the bladder and normal renal function. For these persons, the same principles that promote effective short-course therapy for treatment of acute uncomplicated UTI should also apply. However, clinical studies reported to date do not support the use of short-course therapy for treatment of complicated cystitis. Further studies enrolling well-characterised patient populations with consistent clinical presentations are required to define the role, if any, of short-course therapy in complicated UTI.

Keywords: Urinary tract infection; Antibiotics; Single dose; Short-course therapy

1. Introduction
Urinary tract infection (UTI) has several different clinical presentations [1,2]. Acute uncomplicated UTI or acute uncomplicated cystitis occurs in healthy women with a normal genitourinary tract. This infection is restricted to the bladder. Acute non-obstructive (uncomplicated) pyelonephritis is a kidney infection occurring in this same group of individuals. Escherichia coli is isolated from 80–90% of these infections. Complicated UTI is infection occurring in a person with a structurally or functionally abnormal urinary tract. A wide variety of underlying abnormalities may promote complicated UTI, and clinical presentations vary from cystitis with mild symptoms responding promptly to antimicrobial treatment to septic shock and death in the setting of urinary obstruction. A diverse spectrum of organisms is also isolated from these infections. When obstruction or renal failure is present, infections often cannot be cured despite prolonged antimicrobial courses. Thus, a detailed knowledge of individual patient characteristics is essential for management of urinary infection.

Some authors suggest that all women with diabetes should be considered complicated UTI. However, 5–10% of women with diabetes experience recurrent uncomplicated UTI, similar to the general population. For these episodes, treatment would be similar to women who are not diabetic. Thus, women with diabetes who present with acute symptoms of cystitis may be either uncomplicated or complicated UTI, and management decisions should consider the presence or absence of long-term complications of diabetes, particularly neuropathy. Men may, rarely, experience acute uncomplicated urinary infection. However, this is so uncommon that UTI in a man should always be managed as complicated UTI.

2. Short-course therapy
The kidney is a major organ for removal of some antimicrobials both through glomerular filtration and tubular secretion. The pharmacokinetics relevant to treatment of UTI

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are unique compared with infections at other sites because of the exceptionally high urinary levels that are achieved [3,4]. These high concentrations, together with the presumed superficial nature of bladder infection, provide theoretical support for treatment of cystitis with very brief durations of antimicrobial therapy. Continuing removal of infected urine through adequate voiding also promotes rapid resolution of infection. Short-course antimicrobial therapy, if effective, is preferred because of fewer adverse effects, decreased cost and, potentially, less pressure promoting emergence of antimicrobial resistance in host flora. Short-course therapy also facilitates compliance and patient self-treatment. This paper reviews the current use of short-term therapy for different presentations of UTI, together with some discussion regarding potential future applications.

3. Acute uncomplicated UTI

3.1. Single-dose therapy

Single-dose treatment of acute cystitis has been reported for over 30 years. A variety of antimicrobial agents and dosing regimens are documented to be effective. Outcomes for selected studies, documenting success rates of 80–100%, are shown in Table 1. Trimethoprim/sulfamethoxazole (TMP/SMX), fluoroquinolones and fosfomycin trometamol are clearly highly effective as single-dose therapy for young women with acute uncomplicated cystitis. Generally, β-lactam antimicrobials are less effective, with cure rates of 60–80% reported, although ≥50% of episodes will still be cured with these agents [1].

Despite the well-documented efficacy and substantial early enthusiasm for single-dose therapy, this approach has now fallen into disfavour. Reviews summarising reported clinical trials concluded that single-dose therapy is consistently less successful than more prolonged courses [19–21]. For some antimicrobials, single-dose therapy is equivalent to longer courses at short-term follow-up, but at longer-term outcomes a higher recurrence rate with single-dose therapy is reported. For instance, cure rates at 3 days after therapy with TMP/SMX were 89% for single dose and 92% for 10 days, but at 13 days 24% of the single-dose arm had failed compared with 5% for subjects who received 10 days of therapy [8]. For the single-dose therapy arm, 45% of recurrences were with the initial infecting strain compared with only 5% of recurrences following 10-day therapy. This suggested that single-dose therapy was insufficient to eradicate vaginal and periurethral colonisation, leaving women at risk of early recurrence with persisting uropathogenic *E. coli* strains. For fluoroquinolone antimicrobials, single-dose therapy is highly effective for *E. coli*. The poorer outcomes with single-dose fluoroquinolone therapies reported in some clinical trials may be largely attributable to the lower efficacy of single-dose therapy for *Staphylococcus saprophyticus* infection [9,22]. This is thought to be explained by a more prolonged time required for *S. saprophyticus* killing in urine. Patient and physician acceptance also played a role in disenchantment with single-dose therapy—symptoms continued for several days after the antibiotic dose as inflammation resolved.

Single-dose therapy has not been completely abandoned. Fosfomycin trometamol is licensed as single-dose therapy for acute uncomplicated UTI [12,15]. In clinical trials, this regimen is as efficacious as a 7-day course of norfloxacin.
3.2. Three-day therapy

Three-day therapy has become the standard for treatment of acute uncomplicated cystitis [1,2]. A recent Cochrane review concluded that 3-day therapy is equivalent to longer courses of therapy for clinical outcomes but is less effective for bacteriological outcome [24]. The difference in bacteriological outcome may reflect higher re-infection rates at the follow-up visit given the longer antimicrobial-free follow-up in the 3-day group rather than failure or relapse.

Not all antimicrobials are of equivalent efficacy when given as a 3-day regimen. Some β-lactam antimicrobials, including amoxicillin, amoxicillin/clavulanic acid and oral cephalosporins, consistently have poorer outcomes with 3 days compared with 7–10 days of therapy, even for susceptible organisms [1,25]. This is presumed to reflect a mechanism of action on the cell wall rather than interfering with protein or DNA synthesis. Pivmecillinam, however, is a β-lactam antimicrobial that, at a dose of 400 mg twice a day for 3 days, has equivalent outcomes to 3 days of norfloxacin [26]. With 3-day therapy, nitrofurantoin is 10–15% less effective than TMP/SMX or fluoroquinolones [27], and 7 days of therapy with nitrofurantoin is generally recommended. Thus, recommendations for 3-day treatment must be antimicrobial-specific.

Clinical trials of short-term therapy frequently restrict study entry to pre-menopausal women. When outcomes are stratified by age in studies that include older women, a lower efficacy with short-course therapy for post-menopausal women has been reported [1,24]. Thus, it has been suggested that short-course therapy is not appropriate for post-menopausal women. However, a recent randomised, placebo-controlled, blinded trial enrolled otherwise well ambulatory women over 65 years of age and documented that 3 days of ciprofloxacin was as effective as 7 days for the treatment of acute cystitis [28]. The mean age in the 3-day therapy group was 78.8 years. Clinical and bacterial eradication at 2 days after treatment was 98% for 3-day therapy and 93% for 7 days. Bacterial eradication was 71% and 69%, respectively, at 6 weeks, with relapse and re-infection occurring equally. These study subjects were carefully selected. Women were excluded if there were any signs of systemic infection, any antibiotics taken in the previous 3 days, a creatinine clearance <30 mL/min, structural or functional genitourinary abnormalities, a residual volume >100 mL, an indwelling catheter in the preceding 6 days, diabetes or immunocompromised status. This study provides convincing evidence that 3-day therapy is an acceptable regimen for selected older women.

3.3. The future

Short-course therapy remains an appropriate and attractive option for the treatment of acute uncomplicated cystitis. Wagenlehner et al. [3] recently reported that a single dose of either levofloxacin or extended-release ciprofloxacin had sustained urinary bactericidal titres for common uropathogens for at least 36 h. Studies such as this provide continuing evidence to support short-course therapy, including further assessment of single-dose regimens. Three days of therapy is as effective as longer courses of therapy, is associated with fewer adverse effects and sometimes is less costly. It is well accepted by patients. Given the importance of acute uncomplicated UTI, identification of effective short-course regimens is desirable and further clinical trials evaluating these regimens should be supported. For such clinical trials, however, careful selection of patients and presentations is essential.

The evolution of antimicrobial resistance, particularly the increasing isolation of extended-spectrum β-lactamase-producing E. coli also resistant to TMP/SMX and fluoroquinolones, will require continuing re-assessment of antimicrobial strategies for the treatment of acute uncomplicated urinary infection [29]. Evaluation of any short-course regimen must consider the risks of promoting further resistance in infecting organisms. This is certainly a concern when there is a prolonged half-life with low concentrations persisting in the urine for many days. Ideally, an antimicrobial from a class not used for treating infections at other sites, as is the case for nitrofurantoin, fosfomycin trometamol or pivmecillinam, would be used, so that induction of cross-resistance with other antimicrobials in the class is not a concern.

4. Asymptomatic bacteriuria in pregnancy

Asymptomatic bacteriuria in pregnancy is a unique problem. Treatment of asymptomatic bacteriuria decreases the risk of developing pyelonephritis and the incidence of preterm birth in later pregnancy. This is the only clinical situation, other than prior to urological interventions, when screening for and treatment of asymptomatic bacteriuria is recommended [30]. Bacteriuria in pregnancy may conceptually be considered either uncomplicated or complicated UTI, depending on the time of gestation. Early in pregnancy there is little impact of hormonal changes on the genitourinary tract and treatment considerations would likely be similar to those for uncomplicated UTI. Hormonal effects later in pregnancy lead to decreased autonomic muscle tone and stasis in the genitourinary tract. There is also an increased risk of reflux and obstruction with pressure of the foetal head at the pelvic brim. These physiological changes suggest management of infection later in pregnancy would be similar to complicated urinary infection. An additional consideration is that antimicrobial selection must consider the potential impact on the foetus. Antimicrobial agents considered safe in pregnancy
are nitrofurantoin, β-lactam antimicrobials including both penicillins and cephalosporins, and fosfomycin trometamol.

Despite compelling evidence to support the treatment of asymptomatic bacteriuria in pregnancy, optimal therapeutic regimens are not well defined. A Cochrane review reported that a single dose was as effective as 4–7 days duration for the treatment of bacteriuria in pregnancy [31]. Longer durations of treatment were associated with a significant increase in adverse effects. However, the study numbers were small and there was substantial heterogeneity among the studies. The authors concluded that evidence was insufficient to support definitively single-dose therapy for bacteriuria in pregnancy and that further studies were needed. The question of whether the optimal duration of treatment differs in early or late pregnancy has not been addressed. A recent study reported that single-dose fosfomycin trometamol was equivalent to 5 days of cefuroxime for the treatment of asymptomatic bacteriuria in women during the second trimester, with a cure rate at 1 week of 93% [32]. However, women with pyuria were excluded from this study and the mean gestational age was 16 weeks, which is still relatively early. Further studies evaluating additional regimens are needed to address the question of optimal therapy for bacteriuria in pregnancy.

5. Complicated UTI

5.1. Potential for short-course therapy

Complicated UTI is a diverse clinical syndrome [33]. Frequent recurrent infection characterises these patients if the underlying functional or structural abnormality of the genitourinary tract is not corrected. Recurrence may be re-infection or relapse. Re-infection with a new organism is common, for instance in patients using intermittent catheterisation to assist voiding. Relapse is recurrent infection with the same organism post therapy and is attributed to persistence of the infecting organism in the urinary tract despite antimicrobial therapy. Examples of underlying abnormalities where relapse is anticipated include struvite stones and renal failure. Thus, generalisations for the management of complicated UTI, including duration of therapy, are seldom appropriate. The specific patient population needs to be carefully described.

There are currently no situations where short-course therapy is recommended for treatment of complicated UTI. A recommendation of 7–14 days treatment, depending on clinical presentations, is generally made [2,33]. Within the diversity of presentations of complicated UTI, however, are some patients characterised by adequate urine drainage, infection restricted to the bladder and normal renal function. Infection occurring in these individuals would be anticipated to respond to short-term therapy, similar to the experience with acute uncomplicated UTI. One large group of such patients are those with spinal cord injury and low-pressure voiding maintained through intermittent catheterisation or, for men, sphincterotomy.

5.2. Clinical trials of short-course therapy

5.2.1. Elderly patients

In some early studies exploring management approaches for asymptomatic bacteriuria in elderly institutionalised subjects, the efficacy of single-dose therapy was evaluated [34,35]. Outcomes at 6 weeks for 43 elderly male residents in a long-term care facility given 44 single-dose courses with TMP/SMX or 27 courses of tobramycin were 17% failure, 47% relapse and 36% neither failure nor relapse. Episodes without failure or relapse were associated with a more recent (i.e., ≤4 weeks) onset of infection [34]. In elderly institutionalised women with asymptomatic bacteriuria, 47 courses of single-dose therapy appropriate for the infecting organism were given, including 36 courses of TMP/SMX 320/1600 mg, 4 courses of ampicillin 3 g, 6 courses of tobramycin 100 mg and 1 course of amikacin 500 mg. At 4 weeks 47% of courses had relapsed or failed and by 8 weeks 57%. For courses without relapse or failure, 17% were followed by re-infection at 4 weeks and 32% by 8 weeks. Thus, the microbiological cure rate without relapse, failure or re-infection was only 35% at 4 weeks and 11% at 8 weeks [35]. A trial of single-dose trimethoprim for hospitalised elderly bacteriuric women and men also reported recurrences of 35% at 2 weeks and 70% by 6 weeks [36]. These studies are compelling evidence that single-dose therapy is not effective for treatment of bacteriuria in men or women residents of long-term care facilities.

In a study of 3 days of antimicrobial therapy for male and female residents of a Greek nursing home with relatively good functional status, recurrence rates were 30% at 1 week and 64% at 1 month, with no gender differences [37]. Thus, 3 days of therapy is also not effective for treatment of bacteriuria in the institutionalised elderly. However, it is not clear that more prolonged therapy of 7–14 days has a better outcome than those reported for single-dose or 3-day therapy. Despite these observations relevant to asymptomatic bacteriuria, the efficacy of short-course therapy for symptomatic infection in these populations has not been evaluated in appropriate comparative studies.

5.2.2. Treatment following catheter removal

A single dose was compared with 10 days of therapy in hospitalised women who remained bacteriuric 48 h after removal of a short-term indwelling urethral catheter [38]. Both symptomatic and asymptomatic women had similar outcomes with single-dose or 10-day therapy of TMP/SMX. Women <65 years of age or who had been catheterised for gynaecological surgery were significantly more likely to be cured with either duration of therapy. The single dose was effective for 31 (94%) of 33 women under 65 years of age but only 10 (56%) of 18 women over 65 years.

When 2 days of ciprofloxacin therapy was given routinely to all subjects at catheter removal, irrespective of bacteriuria,
post-therapy symptomatic and asymptomatic UTI was similar for treated and placebo groups [39]. Of concern, the organisms isolated from the treated group were uniformly ciprofloxacin-resistant.

5.2.3. Spinal cord injury

There have occasionally been recommendations for short-term therapy in the treatment of patients with spinal cord injury. One study enrolling both symptomatic and asymptomatic patients reported that 3 days of therapy was as effective as 10 days of therapy [40]. In a prospective, randomised, placebo-controlled trial, 3 days compared with 14 days of ciprofloxacin was evaluated for spinal cord injured patients presenting with lower tract symptoms. The success rate was significantly better (93% vs. 63%) with 14 days of therapy [41]. This difference between the two regimens was fully explained by relapse, both symptomatic and asymptomatic, in the early post-treatment period for patients who received 3 days of therapy. Rates of re-infection were similar for the two treatment durations. Thus, current evidence would not support a general recommendation for short-term antimicrobial treatment of UTI in unselected spinal cord injury patients.

5.3. Future possibilities

These limited studies provide evidence that short-course therapy is not appropriate for many patients with complicated UTI, but some patients are effectively treated with these regimens. Whilst the study enrolling spinal cord injured patients suggested that more prolonged courses of therapy would, overall, result in a better outcome, a role for short-term therapy for selected patients is not excluded. In addition, a sequential approach with initial treatment with 3 days of therapy and subsequent re-treatment with a more prolonged course if symptomatic relapse occurs could be evaluated. Short-course therapy may be effective for subjects with a shorter duration of symptoms. The impact of therapy duration on emergence of resistance must also be considered. There is a need for clinical studies on the treatment duration for complicated UTI. These studies should enrol well-characterised populations with respect to the underlying genitourinary abnormality. The outcomes of therapy must be stratified by the underlying abnormality as well as presumed upper or lower tract infection and, if recurrent infection is being treated, whether this is relapse or re-infection. Such studies may well be difficult to perform because of the need for careful patient selection and the relatively small number of subjects likely to be eligible to be enrolled for a given abnormality and presentation.

6. Conclusions

In this era of considerable evidence for and concern about antimicrobial overuse, treatment of UTI may provide some options to limit antimicrobial pressure through relatively brief durations of therapy. It is clear that minimal therapy with even a single dose is effective for the majority of healthy women with acute uncomplicated UTI, although this therapy is marginally less effective than therapy of a longer duration. Whilst available studies suggest that single-dose therapy may be an option for the treatment of asymptomatic bacteriuria in pregnancy, further clinical trials are needed to confirm the effectiveness of this approach. Identifying which of the wide spectrum of individuals with complicated UTI may benefit with short-course therapy also requires further critical evaluation through carefully designed and conducted clinical trials.

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References


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