

# Therapeutics Initiative

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## Empiric Antibiotic Therapy for Uncomplicated Lower Urinary Tract Infections

Urinary tract infections (UTIs) are one of the most common clinical conditions of women in primary care. This Letter describes antimicrobial best practices for the treatment of symptomatic, uncomplicated lower UTI in British Columbia (BC), Canada.

UTIs in most healthy women who are not pregnant and have no major abnormality of urinary tract structure and function, can be considered “uncomplicated.”<sup>1,2</sup> This Letter does not discuss complicated lower UTI (e.g. in men), upper urinary tract infections (e.g. pyelonephritis), recurrent UTI, nor asymptomatic bacteriuria.

### Diagnose by symptoms, not tests

A diagnosis of lower uncomplicated UTI (or “acute cystitis”) can be made with > 90% probability if a patient is experiencing two or more of dysuria, urgency, or frequency, and no vaginal discharge.<sup>3</sup> As women age, genitourinary symptoms less reliably predict uncomplicated UTI.<sup>2</sup>

If the clinical symptoms are uncertain, a urine dipstick test showing the presence of nitrites and moderate pyuria may help rule-in the diagnosis.<sup>4</sup> However, dipstick tests are less helpful for ruling-in the diagnosis in older women; asymptomatic bacteriuria, and corresponding dipstick abnormalities, increase with age.<sup>4</sup>

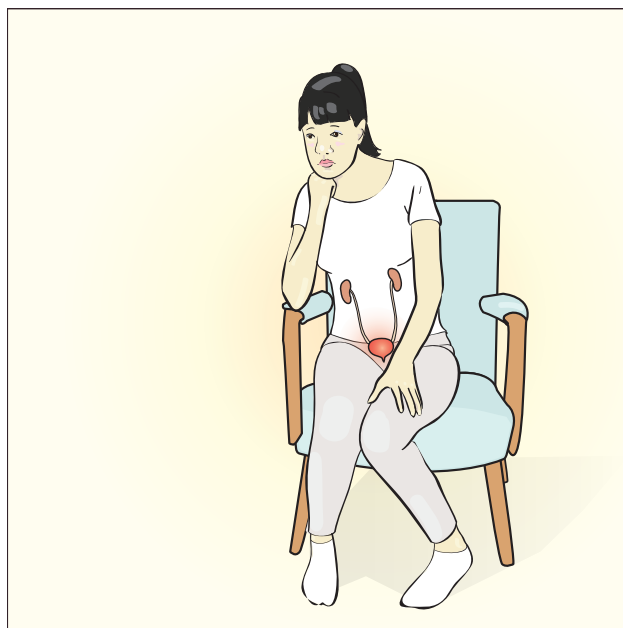
### Culture seldom required

Fewer than 2% of urine cultures meaningfully impact choice of treatment or need for follow-up.<sup>5</sup> Thus, **most major guidelines recommend against culture for symptomatic uncomplicated UTI.**<sup>5,6</sup> In one randomized controlled trial (RCT) neither a urine dipstick nor a culture, compared with empiric therapy, improved symptom outcomes or time to re-consultation; serious outcomes were not reported.<sup>7</sup>

The BC Centre for Disease Control (BCCDC) recommends urine cultures prior to treatment only in specific situations: suspicion of complicated and upper UTI (i.e. pyelonephritis), previous UTI with specific resistant organisms, recent travel outside of Canada/USA, recent quinolone or cephalosporin use, and recent hospitalization.<sup>8</sup> (see Bugs and Drugs [www.bugsanddrugs.org](http://www.bugsanddrugs.org) for further detail) **Post-treatment urine cultures are not recommended** after achieving clinical cure.<sup>9</sup>

### Treat with regard to regional resistance patterns

A Cochrane systematic review found that various antibiotics achieve similar resolution of symptoms of uncomplicated UTIs and recommended that antibiotic treatment should reflect local bacterial resistance patterns.<sup>10</sup>



*E. coli* is the pathogen in about 80% of uncomplicated UTIs.<sup>11</sup> In BC during 2019, only 3.5% of *E. coli* isolated from urine were nitrofurantoin resistant.<sup>12</sup> More frequent use of nitrofurantoin has not increased *E. coli* resistance in BC or other jurisdictions.<sup>12,13</sup>

In contrast, *E. coli* resistance to ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) in BC exceeds 20%. Amoxicillin resistance (based on ampicillin resistance, which is equivalent) exceeds 40%, and cephalexin resistance exceeds 50%.<sup>12</sup> The Infectious Diseases Society of America (IDSA) recommends against using antibiotics for organisms with resistance rates to specific drug classes over 20%, or over 10% in the case of fluoroquinolones. The IDSA states that **fluoroquinolones have a propensity for collateral damage and should be reserved for important uses other than acute cystitis.**<sup>1</sup>

### Nitrofurantoin for 5-7 days best for uncomplicated UTI in BC

Nitrofurantoin (MacroBID 100 mg BID or MacroDantin 50 mg qid) provides the best combination of clinical effectiveness, low bacterial resistance, and infrequent adverse events. Courses of 5 to 7 days have superior efficacy (~79 to 92%) compared with 3 days (~61 to 70%). Two meta-analyses focusing on nitrofurantoin for uncomplicated UTI both demonstrated that nitrofurantoin achieves symptom resolution equivalent to other antibiotics, with similar or fewer adverse events.<sup>14,15</sup>

Common adverse effects of nitrofurantoin include discolouration of urine, nausea (8%), and headache (6%).<sup>16</sup> No severe irreversible outcomes were noted with up to 14 days of treatment in RCTs (N=4807).<sup>14</sup> Observational studies and models report acute, reversible interstitial pneumonitis in 1 per 5000 people, usually beginning within 3-8 days of first use, and resolving shortly after stopping.<sup>17,18</sup>

Hepatotoxicity and pulmonary fibrosis occurred almost exclusively in people taking nitrofurantoin for > 6 months.<sup>19</sup>



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## What is the alternative for patients unable to take nitrofurantoin?

Nitrofurantoin is excreted into the urine. It is not recommended if creatinine clearance is  $\leq 30$  milliliters/minute as its efficacy decreases, while toxicity increases.<sup>20,21</sup>

The BCCDC recommends a single oral dose of fosfomycin 3 g as the preferred alternative to nitrofurantoin. It reaches high urinary but low systemic concentration and is effective even in patients with decreased creatinine clearance.<sup>22,23</sup>

A systematic review of fosfomycin compared with other antibiotics found equivalent clinical cure and no significant differences in adverse effects.<sup>24</sup>

In BC, the majority of *E. coli* are considered susceptible to fosfomycin, although current susceptibility testing methods are unable to detect all mechanisms of resistance. There is concern that overuse of fosfomycin in uncomplicated UTI may promote more widespread resistance, but to date this has not been demonstrated.<sup>25</sup> Fosfomycin is costlier for a therapeutic course (PharmaCare pays \$12.64 for a 3-gram packet) than nitrofurantoin (\$6.44 for 5 days of therapy).

## Antibiotic treatment failure

Observational studies in the United Kingdom found that 12 to 16% of patients treated for uncomplicated UTI returned within a month with urinary symptoms, regardless of the initial antibiotic.<sup>26</sup> They may require a detailed history, urine culture, and other investigations to determine best care.

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## Non-antibiotic treatment

Spontaneous improvement of uncomplicated UTI occurs in 33-50% of women.<sup>27</sup> While some RCTs have assessed the use of cranberry supplements and increased hydration for prevention of UTI, none assessed them as **therapies for UTI**.<sup>28</sup>

Shared decision-making can include options for delayed antibiotic prescriptions or symptom management with NSAIDs. A meta-analysis of antibiotic treatment versus placebo found no difference in pyelonephritis in the two RCTs that reported this outcome.<sup>29</sup> However, two subsequent RCTs comparing NSAID versus antibiotic treatment in outpatients reported worse results for the NSAID groups.<sup>30,31</sup>

## Conclusions

- Urine dipstick/urinalysis and/or urine cultures are not recommended for diagnosing uncomplicated lower urinary tract infections.
- Empiric prescription of nitrofurantoin for 5 to 7 days is recommended.
- The BCCDC recommends one oral dose of fosfomycin 3 g when CrCl is  $\leq 30$  mL/min or when there is allergy/intolerance to nitrofurantoin.
- TMP-SMX, fluoroquinolones, and beta-lactams are unsuitable for empiric therapy in BC due to bacterial resistance.

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