Antimicrobial resistance in community-acquired *Escherichia coli* isolated from urinary infection: Good news or bad?

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Urinary tract infection remains a common and important bacterial infection among adults. Symptomatic urinary infection occurring in nonpregnant women with a normal genitourinary tract is considered to be acute uncomplicated urinary tract infection (1). This syndrome occurs most frequently in young women, but older women, particularly in the early postmenopausal period, also experience acute uncomplicated infection. Complicated urinary tract infection occurs in women or men of all ages with functional or structural abnormalities of the urinary tract. The heterogeneity of clinical presentations of urinary tract infection requires different management strategies for different populations.

Escherichia coli is the single most important organism causing urinary infection. Increasing antimicrobial resistance among *E coli* strains circulating in community populations is an important issue relevant to antimicrobial strategies for treatment of urinary infection (2). Community-acquired *E coli* resistance to fluoroquinolones and the emergence of extended-spectrum beta-lactamase (ESBL)-producing strains are now of particular concern. Organisms with increased antimicrobial resistance are isolated more frequently from individuals with complicated urinary tract infection (3). This is a consequence of acquisition of organisms following health care exposures, together with repeated previous antimicrobial courses for many patients with persistent abnormalities who experience recurrent infection. Some women with frequent recurrent acute uncomplicated urinary tract infection also receive repeated antimicrobial courses, which may promote the emergence of antimicrobial-resistant *E coli* in the gut flora. However, the increasing antimicrobial resistance reported in community-acquired *E coli* infection has many other potential sources. Uropathogenic *E coli* are usually acquired from environmental exposures including sexual partners, household members, pets, food and, frequently, during travel. There is widespread dissemination of resistant uropathogenic *E coli* clones nationally and globally (4,5). A study from Calgary (Alberta) within the past decade describes isolation of ESBL-producing *E coli* from urine specimens submitted to a central laboratory and reported a strong association of isolation of these strains with travel, particularly to India and the Middle East (6).

The current management of acute uncomplicated cystitis involves empirical treatment on the basis of symptom presentation without obtaining a urine specimen for culture (2). This approach is based on several characteristic features of this syndrome. These include the high reliability of symptom presentation for accurate clinical diagnosis; the uniform microbiology, with 75% to 85% of episodes caused by *E coli*; the efficacy of short-course antimicrobial regimens, meaning that urine culture results are often not available until antimicrobial treatment is completed; and the difficulty of applying the usual standard for quantitative urine culture when 25% of women with this syndrome have a count of $<10^8$ colony-forming units/L of organisms isolated in the urine (1,2). A pretherapy urine culture is, however, recommended before antimicrobial therapy if there is diagnostic uncertainty, if the patient has failed to respond to initial appropriate empirical therapy or

when there is an early symptomatic recurrence following therapy (1). Recent international guidelines recommend empirical treatment with three days of trimethoprim/sulfamethoxazole (TMP/SMX), five days of nitrofurantoin, a single dose of fosfomycin, or three to five days of pivmecillinam (2). For this empirical approach to be effective, practitioners must have knowledge of the local prevalence of antimicrobial resistance to the potential first-line empirical antimicrobials. If the prevalence of resistance of *E coli* strains to a given antimicrobial is $>20\%$, that agent is not considered to be appropriate for empirical first-line therapy for uncomplicated urinary infection.

TMP/SMX has been a mainstay of empirical treatment for acute cystitis in women since its introduction in the 1980s. The prevalence of resistance to TMP/SMX in community-acquired uropathogenic *E coli* strains has been increasing globally and, in many areas of the world, is currently above 20% (7,8). An important question, then, is: What is the current susceptibility of community-acquired *E coli* to TMP/SMX in Canada? Previous Canadian studies reported a prevalence of resistance to TMP/SMX for community isolates collected in 2002 of 10.8%, varying from 0% in the east to 24% in the west (9). Another study involving isolates submitted to clinical laboratories from family physicians' offices in 2004 reported 15.2% TMP/SMX resistance, varying from 11.4% in the Atlantic provinces to 20.5% in British Columbia (10). The regional variation observed for Canada in these studies reinforces the need for local resistance prevalence data. However, antimicrobial resistance is dynamic and periodic monitoring is necessary to ensure reliable and timely information.

Surveillance data that accurately describe the antimicrobial susceptibility of *E coli* isolated from women with acute uncomplicated urinary tract infection are, however, not readily available (11). The recommended practice of treatment without obtaining a urine specimen for culture means that clinical laboratories receive few specimens from women presenting to community family practitioners with straightforward acute cystitis. Urine specimens for culture are more frequently submitted from women in whom there is a higher likelihood of resistance. These are women with complicated urinary tract infection as well as those with uncomplicated infection who have failed to respond adequately to initial empirical therapy, potentially because resistant organisms are present. Thus, the prevalence of *E coli* resistance reported for urine specimens submitted to diagnostic microbiology laboratories overestimates the true resistance of strains causing uncomplicated infection. To reliably map the progression and variability of antimicrobial resistance in community-acquired uropathogenic *E coli* requires dedicated surveys collecting urine specimens systematically from unselected women presenting with truly uncomplicated infection.

In the current issue of the *Journal*, McIsaac et al (12) (pages 143-149) report the national and regional antimicrobial resistance prevalence of *E coli* isolated from urine specimens of women with presumed acute uncomplicated infection presenting to family practitioners across Canada. Specimens evaluated were collected between 2009 and

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2011. The study reports an increased prevalence of TMP/SMX and ciprofloxacin resistance compared with the same authors' 2002 survey (9), and some variation in susceptibility across the country. The Canadian TMP/SMX antimicrobial resistance prevalence is 16%, with the highest rates of 20% for British Columbia and 21.1% for the prairies. However, neither the differences reported between this and the 2002 survey nor the regional variation were significant. Other important observations include increased ciprofloxacin resistance from 1.1% in 2002 to 5.5% for all isolates, with a remarkable increase from 0% to 18% in British Columbia. The universal susceptibility of strains to nitrofurantoin and the isolation of only a single ESBL-producing *E. coli* strain are both reassuring.

There are several surprising observations. The TMP/SMX resistance rate of 21.1% reported for the prairies has, in fact, fallen from the rate of 27.8% reported in 2002. Quebec and the Maritimes also have a slight decreased prevalence of ciprofloxacin resistance, from 7.7% to 5.7%, although the number of isolates is small. The TMP/SMX resistance rate for older subjects was one-half that of younger women, which is at variance with most other surveys, which suggest increased resistance is more common in older women. No explanation is offered for these somewhat anomalous observations. The differences may simply reflect the small number of isolates from some regions. In addition, the prevalence of resistance is a function of antimicrobial pressure. Decreased use of TMP/SMX for urinary infection could explain some of the observations. The authors provide no information describing travel exposures; therefore, the impact of this important variable cannot be addressed.

Are the observations from this survey reliable enough to direct choices for empirical therapy for women with acute uncomplicated urinary tract infection? The reported TMP/SMX resistance prevalence for British Columbia and the prairies does, barely, exceed the 20% mark, so this is a relevant question. The reported prevalence should, however, be interpreted with caution for several reasons. Almost 40% of subjects had comorbidities, including subjects with neurogenic bladder, catheters and predisposing anatomical factors consistent with complicated urinary tract infection. There were no significant differences in antimicrobial susceptibility between subjects with or without comorbidity, but a consistent trend is present. For TMP/SMX, resistance was 14% without and 22% with comorbidity, for ampicillin 27% and 40%, and for ciprofloxacin 4% and 8%, respectively. Inclusion of these isolates is not appropriate if the observations are to be interpreted in the context of recommendations for treatment of uncomplicated infection.

The generalizability of the observations, even for women without comorbidities, is uncertain. Only 4.5% of invited physicians agreed to participate, and only one-half of these provided at least one case. There is also likely bias in patient selection, which could inflate the resistance prevalence estimates. Physicians were asked to assess up to four women chosen at their discretion. It is reasonable to assume that, given this discretion, physicians may have been more likely to obtain specimens from women in whom the diagnosis was not straightforward or management was problematic. It is not clear how many of the women who were approached to participate provided consent, but of those who did provide consent urine culture reports were obtained from only 57%. Again, a reasonable conclusion is that women who were more concerned about their urinary tract infection, ie, those with more prolonged symptoms, more frequent recurrences or less satisfactory response to previous antimicrobial therapy, all of whom may be more likely to have resistant isolates, would have been more interested in participating.

Thus, selection bias may favour inclusion of women with an increased possibility of more resistant organisms, and the reported rates are likely overestimates of the true resistance of *E. coli* causing acute uncomplicated cystitis. This suggests that TMP/SMX remains an appropriate empirical treatment for acute cystitis in healthy women in

Canada, even in regions where the reported prevalence in this survey was 20%. Despite efforts to sample women across Canada, 51.6% of isolates were from Ontario and many provinces were represented by a small number of isolates – for instance, only eight from Prince Edward Island and eight from Saskatchewan. This restricts the utility of these observations at the local level for most regions. In addition, intraprovincial variation, particularly for unique populations such as isolated northern communities where resistance may differ substantially from elsewhere in a province, was not assessed.

However, the report by McIsaac et al (12) provides several important observations. First, as elsewhere in the world, an increasing prevalence of resistance to some of the common antimicrobials used for urinary tract infection, including fluoroquinolones, is apparent. Despite this, the reported levels of TMP/SMX resistance support continued empirical use of this agent for acute uncomplicated urinary infection. The regional variation observed underscores the importance of local prevalence data. Observations of decreased resistance to TMP/SMX in the prairies and to fluoroquinolones in the Atlantic region are intriguing, but of uncertain validity. ESBL-producing strains are not yet common in Canada, and nitrofurantoin remains an effective choice for first-line empirical therapy for acute uncomplicated cystitis. The study also highlights the need for reliable surveillance systems to monitor susceptibility of community-acquired bacterial pathogens, including uropathogenic *E. coli*, to support optimal therapy and contribute to preservation of the effectiveness of antimicrobials for the treatment of common bacterial infections.

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