

## Guidelines for the diagnosis and management of recurrent urinary tract infection in women

Shawn Dason,\* Jeyapandy T. Dason, MBBS, CCFP;† Anil Kapoor, MD, FRCSC\*

\*Division of Urology, Department of Surgery, McMaster University, Hamilton, ON; †Department of Family Medicine, McMaster University, Hamilton, ON

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### Introduction

Recurrent uncomplicated urinary tract infection (UTI) is a common presentation to urologists and family doctors. Survey data suggest that 1 in 3 women will have had a diagnosed and treated UTI by age 24 and more than half will be affected in their lifetime.<sup>1</sup> In a 6-month study of college-aged women, 27% of these UTIs were found to recur once and 3% a second time.<sup>2</sup>

The following topics are reviewed in this guideline. We also include a summary of recommendations (Text box 1).

1. Definition of recurrent uncomplicated UTI
2. Diagnosis of recurrent uncomplicated UTI
3. Investigation of recurrent uncomplicated UTI
4. Indications for specialist referral
5. Prophylactic measures against recurrent uncomplicated UTI

### Methods

Recommendations are made based on systematic searches of *Ovid MEDLINE*, the *Cochrane Library*, *EMBASE* and *MacPLUS FS*. Where applicable, English studies based on humans from 1980 to April 2011 were included. The following guidelines were also reviewed: *Society of Obstetricians and Gynecologists of Canada (SOGC, 2010)*,<sup>3</sup> *European Association of Urology (EAU, Updated 2010)*,<sup>4</sup> *American College of Radiology (ACR, Updated 2011)*<sup>5</sup> and *American College of Obstetrics and Gynecology (ACOG, 2008)*.<sup>6</sup>

### Definitions

A UTI reflects an infection of the urinary system causing an inflammatory response. Only bacterial infections will be reviewed in this document. A UTI occurs when the normal

flora of the periurethral area are replaced by uropathogenic bacteria, which then ascend to cause a bacterial cystitis. Infrequently, this infection ascends to the kidney to cause a bacterial pyelonephritis. Ascending infection is thought to be caused by bacterial virulence factors allowing for improved adherence, infection and colonization by uropathogens. The usual uropathogens include *Escherichia coli*, *Staphylococcus saprophyticus*, *Klebsiella pneumoniae* and *Proteus mirabilis*.<sup>7</sup>

A UTI may be recurrent when it follows the complete clinical resolution of a previous UTI.<sup>8</sup> A threshold of 3 UTIs in 12 months is used to signify recurrent UTI.<sup>3</sup> The pathogenesis of recurrent UTI involves bacterial reinfection or bacterial persistence, with the former being much more common.<sup>8</sup> In bacterial persistence, the same bacteria may be cultured in the urine 2 weeks after initiating sensitivity-adjusted therapy. A reinfection is a recurrence with a different organism, the same organism in more than 2 weeks after treatment, or a sterile intervening culture.<sup>9</sup> Although culture remains the gold standard for diagnosis of recurrent uncomplicated UTI, clinical discretion should be applied in accepting a history of positive dipstick tests, microscopy and symptomatology as surrogate markers of UTI episodes.

An uncomplicated UTI is one that occurs in a healthy host in the absence of structural or functional abnormalities of the urinary tract.<sup>10</sup> All other UTIs are considered complicated UTIs (Table 1). Although uncomplicated UTI includes both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated etiology.

### Diagnosis

#### Clinical

Physicians should document symptoms patients consider indicative of a UTI, results of any investigations, and responses to treatment. Positive culture, regardless of defini-

**Table 1. Host factors that classify a urinary tract infection as complicated**

Complication	Examples
Anatomic abnormality	Cystocele, diverticulum, fistula
Iatrogenic	Indwelling catheter, nosocomial infection, surgery
Voiding dysfunction	Vesicoureteric reflux, neurologic disease, pelvic floor dysfunction, high post void residual, incontinence
Urinary tract obstruction	Bladder outlet obstruction, ureteral stricture, ureteropelvic junction obstruction
Other	Pregnancy, urolithiasis, diabetes or other immunosuppression

tion, is predicted by symptoms of dysuria, frequency, urgency, hematuria, back pain, self-diagnosis of UTI, nocturia, costovertebral angle tenderness and the absence of vaginal discharge or irritation.<sup>11,12</sup> Factors that predispose to recurrent uncomplicated UTI include menopause, family history, sexual activity, use of spermicides and recent antimicrobial use.<sup>13,14</sup> A physical examination, including pelvic examination, should also be performed. The history and physical examination should be focused on ruling out structural or functional abnormalities of the urinary tract (complicated UTI) (Table 1).<sup>15</sup>

If available, postvoid residual and uroflowmetry are optional tests in postmenopausal women. In a study of 149 postmenopausal women with recurrent uncomplicated UTI and 53 age-matched controls, higher postvoid residual (23% recurrent UTI vs. 2% control,  $p < 0.001$ ) and reduced urine flow (45% recurrent uncomplicated UTI vs. 23% control,  $p = 0.004$ ) were present in women with recurrent uncomplicated UTI.<sup>16</sup> In combination with other clinical parameters, abnormalities in these tests may suggest complicated UTI (Table 1). In comparison, a study of 213 non-pregnant women aged 18-30 by Hooton and colleagues found no significant difference in postvoid residual volume and urine flow rates between women with recurrent uncomplicated UTI and controls.<sup>17</sup>

## Laboratory

When working up recurrent uncomplicated UTI, culture and sensitivity analysis should be performed at least once while the patient is symptomatic. This workup confirms a UTI as the cause for the patient's recurrent lower urinary tract symptoms. Additionally, adjustment of empirical therapy based on sensitivity may eradicate resistant bacteria as a cause for bacterial persistence and recurrent UTI.

A midstream urine bacterial count of  $1 \times 10^5$  CFU/L should be considered a positive culture while the patient is symptomatic.<sup>12</sup> Potential for contamination with midstream

**Table 2. Indications for further investigation of recurrent urinary tract infection**

Prior urinary tract surgery or trauma
Gross hematuria after resolution of infection
Previous bladder or renal calculi
Obstructive symptoms (straining, weak stream, intermittency, hesitancy), low uroflowmetry or high PVR
Urea-splitting bacteria on culture (e.g., Proteus, Yersinia)
Bacterial persistence after sensitivity-based therapy
Prior abdominopelvic malignancy
Diabetes or otherwise immunocompromised
Pneumaturia, fecaluria, anaerobic bacteria or a history of diverticulitis
Repeated pyelonephritis (fevers, chills, vomiting, CVA tenderness)
Asymptomatic microhematuria after resolution of infection should be evaluated as per CUA guidelines <sup>25</sup>

PVR: post-void residual CVA: costovertebral angle; CUA: Canadian Urological Association.

urine collection necessitates careful evaluation of the cultured species reported. A negative culture, while maintaining a response to treatment, may be present in a minority of women.<sup>18</sup> A negative culture and lack of response to treatment suggest another diagnosis. Patients may then be re-cultured 1 to 2 weeks after initiating therapy adjusted to sensitivity to evaluate for bacterial persistence.

## Further investigation

Several studies have demonstrated a very low incidence of anatomical abnormalities (0 to 15%) on cystoscopy performed for recurrent UTI.<sup>19-24</sup> It, therefore, seems unnecessary to perform cystoscopy on all women presenting with recurrent uncomplicated UTI given this low pre-test probability. The small size of these studies prevented univariate or multivariate analysis to evaluate pre-test risk factors for an abnormal cystoscopy. Nonetheless, some factors suggest complicated UTI and warrant cystoscopy (Table 2).

Imaging in the setting of all women with recurrent UTI is also unnecessary with a low pre-test probability of complicated UTI (absence of criteria in Table 2). Several series demonstrate a low yield of non-incident findings following imaging for recurrent UTI and it is not routinely recommended by the Society of Obstetricians and Gynecologists of Canada (SOGC), American College of Radiology (ACR), European Association of Urology guidelines.<sup>3,5,9,20-24</sup>

When there is high clinical suspicion of an abnormality (Table 2), a computed tomography image of the abdomen and pelvis with and without contrast is the best imaging technique for detecting causes of complicated UTI.<sup>25</sup> To minimize radiation exposure, ultrasound imaging of the urinary tract with an optional abdominal X-ray is also appropriate.<sup>26-31</sup> Imaging to rule out specific causes of UTI (Table 1) is optimized in consultation with a radiologist or the 2011 ACR guidelines.<sup>5</sup>

**Table 3. Suggested antibiotic prophylaxis<sup>39</sup>**

Continuous	Postcoital (within 2 hours of coitus)
Trimethoprim/sulfamethoxazole (TMP/SMX) (40 mg/200 mg daily or thrice weekly) <sup>45</sup>	TMP/SMX (40 mg/200 mg to 80 mg/400 mg) <sup>46</sup>
Trimethoprim (100 mg daily) <sup>45,47</sup>	
Ciprofloxacin (125 mg daily) <sup>48</sup>	Ciprofloxacin (125 mg) <sup>48</sup>
Cephalexin (125 mg to 250 mg daily) <sup>49</sup>	Cephalexin (250 mg) <sup>50</sup>
Cefaclor (250 mg daily) <sup>51</sup>	
Nitrofurantoin (50 mg to 100 mg) <sup>52</sup>	Nitrofurantoin (50 mg–100 mg daily) <sup>46</sup>
Norfloxacin (200 mg daily) <sup>53</sup>	Norfloxacin (200 mg) <sup>56</sup>
Fosfomycin (3 g every 10 days) <sup>55</sup>	
	Ofloxacin (100 mg) <sup>56</sup>

**Indications for specialist referral**

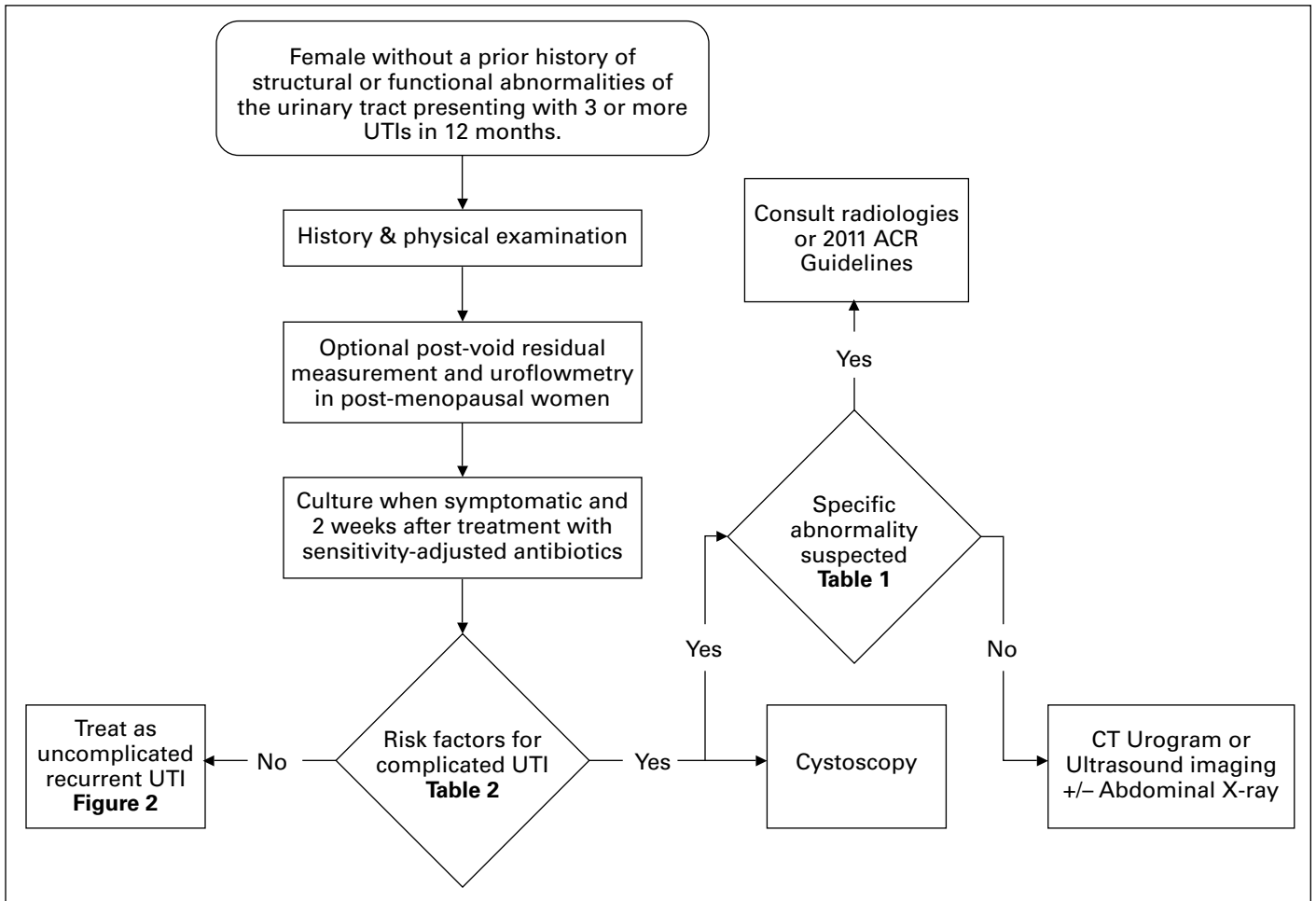
Most patients with recurrent uncomplicated UTI may be treated successfully by family physicians.<sup>32</sup> Specialist referral for recurrent uncomplicated UTI is indicated when risk

factors for complicated UTI are present (Table 2). Referral is also indicated when a surgically correctable cause of UTI is suspected (Table 1) or the diagnosis of UTI as a cause for recurrent lower urinary tract symptoms is uncertain. Prior to referral, culture of the urine while symptomatic and 2 weeks after sensitivity-adjusted treatment may aid in confirming the diagnosis of UTI, as well as guiding further specialist evaluation and management.

**Management**

**Conservative measures**

No good evidence exists for conservative measures in preventing recurrent UTI. Patients may be counselled on modifiable predisposing factors for UTI, including sexual activity and spermicide use.<sup>14,33-35</sup> Voiding before or after coitus is also unlikely to be harmful, but there is no evidence for this practice.<sup>36</sup> The evidence behind lactobacillus probiotics in UTI prophylaxis is also inconclusive.<sup>37,38</sup>



**Fig. 1.** Evaluation of recurrent urinary tract infection.

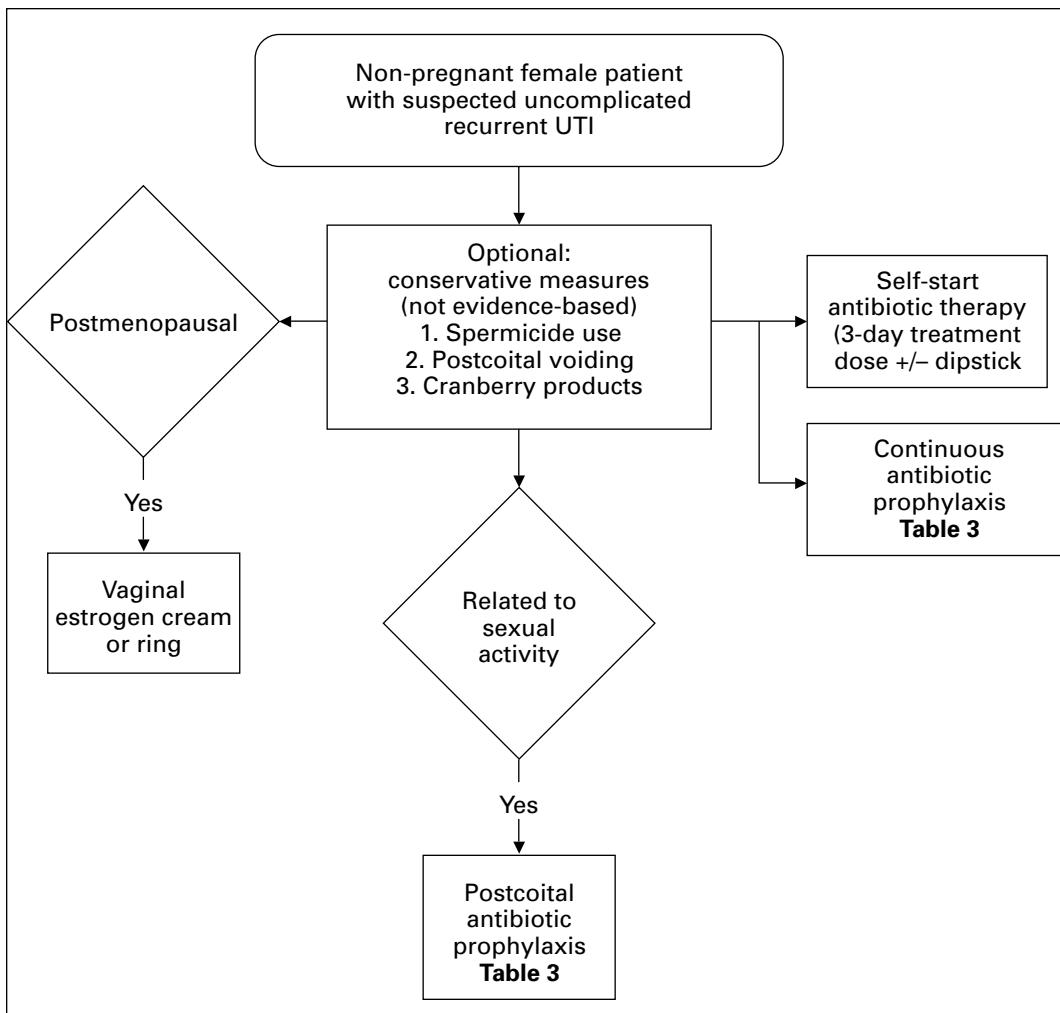


Fig. 2. Management of recurrent urinary tract infection.

Evidence for the effectiveness of cranberry products to prevent UTI is conflicting and no recommendation can be made for or against their use. A Cochrane Database systematic review updated in 2008 suggested that there is some evidence cranberry products may prevent recurrent UTI in women.<sup>39</sup> This was based on randomized placebo-controlled trials by Stothers<sup>40</sup> and Kontiokari and colleagues<sup>41</sup> demonstrating a pooled relative risk of 0.61 (95% CI 0.40-0.91) favouring cranberry over placebo in 241 pooled patients. In 2011, a randomized placebo-controlled trial of cranberry juice versus placebo juice with 319 participants showed no significant difference in UTI recurrence rates between these two groups.<sup>42</sup> Various criticisms have been made of each of these studies.<sup>9,39,42</sup>

## Antibiotics

### *Continuous low-dose antibiotics*

Continuous low-dose antibiotic prophylaxis is effective at preventing UTIs. A 2008 Cochrane Database systematic

review pooled 10 trials enrolling 430 women in evaluating continuous antibiotic prophylaxis versus placebo.<sup>43</sup> A meta-analysis of these trials demonstrated that the relative risk for clinical recurrence per patient-year (CRPY) was 0.15 (95% CI 0.08-0.28) favouring antibiotics. The relative risk for severe side effects (requiring treatment withdrawal) was 1.58 (95% CI 0.47-5.28) and other side effects was 1.78 (95% CI 1.06-3.00) favoring placebo. Side effects included vaginal and oral candidiasis, as well as gastrointestinal symptoms. Severe side effects were most commonly skin rash and severe nausea. No additional trials were identified refuting this systematic review.

Because the optimal prophylactic antibiotic is unknown, allergies, prior susceptibility, local resistance patterns, cost and side effects should determine the antibiotic choice.<sup>39</sup> Nitrofurantoin followed by cephalexin display the highest rates of treatment dropout.<sup>39</sup> Prior to prophylaxis, patients should understand the potential for common side effects and the fact that severe side effects do occur rarely with all antibiotics.<sup>44</sup>

**Text box 1. Summary of recommendations****1. Definition of recurrent uncomplicated UTI**

- a. An uncomplicated UTI is one that occurs in a healthy host in the absence of structural or functional abnormalities of the urinary tract. Recurrent uncomplicated UTI may be defined as 3 or more uncomplicated UTIs in 12 months (Level 4 evidence, Grade C recommendation).
- b. Recurrent UTIs occur due to bacterial reinfection or bacterial persistence. Persistence involves the same bacteria not being eradicated in the urine 2 weeks after sensitivity-adjusted treatment. A reinfection is a recurrence with a different organism, the same organism in more than 2 weeks, or a sterile intervening culture (Level 4 evidence, Grade C recommendation).

**2. Diagnosis of recurrent uncomplicated UTI**

- a. Clinical diagnosis of each UTI episode is supported by symptoms of dysuria, frequency, urgency, hematuria, back pain, self-diagnosis of UTI, nocturia, costovertebral tenderness and the absence of vaginal discharge or irritation (Level 1 evidence, Grade A recommendation).
- b. Complicated causes of UTI may also be ruled out on history and physical examination (Table 1). Uroflowmetry and determining post void residual are optional tests in postmenopausal women to exclude complicated causes of UTI (Level 3 evidence, Grade C recommendation).
- c. Culture and sensitivity analysis should be performed when symptomatic and in 2 weeks from sensitivity-adjusted treatment to confirm UTI, guide further treatment and exclude persistence. (Level 4 evidence, Grade C recommendation)

**3. Investigation of recurrent uncomplicated UTI**

- a. Cystoscopy and imaging are not routinely necessary in all women with recurrent UTI (Level 2 evidence, Grade B recommendation).
- b. Women with risk factors (Table 2) for a complicated cause for recurrent urinary tract infection should be evaluated by cystoscopy and imaging. Women suspected of having a complicated UTI (Table 2) without knowledge of a specific abnormality (Table 1) should receive a CT urogram or abdominopelvic ultrasound +/- abdominal x-ray. Women suspected of having a specific cause of UTI (Table 1) should be imaged in consultation with a radiologist or the 2011 ACR guidelines (Level 4 evidence, Grade C Recommendation).

**4. Indications for specialist referral**

- a. Specialist referral is recommended for investigation of women with risk factors for complicated UTI (Table 2), surgical correction of a cause of UTI (Table 1), or when the diagnosis of recurrent uncomplicated UTI is uncertain (Level 4 evidence, Grade C Recommendation).

After discontinuing prophylaxis, women were found to revert to their previous frequency of UTI. Pooling 2 studies demonstrated a 0.82 relative risk (95% CI 0.44-1.53) of microbiologic recurrence per patient-year relative to placebo after discontinuing prophylaxis.<sup>39</sup> Six to 12 months of therapy was used in trials demonstrating a benefit; there is no clear evidence to guide treatment after this point, although low-dose trimethoprim/sulfamethoxazole has been tried for up to 5 years.<sup>57</sup> If patients wish to continue antibiotic prophylaxis for longer periods, they should be advised that there is no long-term safety data for this and there is a small chance of severe side effects<sup>44</sup> and resistant breakthrough infections.<sup>9</sup>

**5. Prophylactic measures against recurrent uncomplicated UTI**

- a. Conservative measures including limiting spermicide use and postcoital voiding lack evidence for their efficacy but are unlikely to be harmful (Level 4 evidence, Grade C recommendation).
- b. Cranberry products have conflicting evidence for their efficacy (Level 1 evidence, Grade D recommendation).
- c. Continuous antibiotic prophylaxis (Table 3) is effective at preventing UTI. (Level 1 evidence, Grade A recommendation).
- d. Postcoital antibiotic prophylaxis (Table 3) within 2 hours of coitus is also effective at preventing UTI (Level 1 evidence, Grade A recommendation).
- e. Self-start antibiotic therapy with a 3-day treatment dose antibiotic at the onset of symptoms is another safe option for the treatment of recurrent uncomplicated UTI (Level 1 evidence, Grade A recommendation).
- f. Vaginal estrogen creams or rings may also reduce the risk of clinical UTI relative to placebo or no treatment in postmenopausal women (Level 1 evidence, Grade A recommendation).
- g. Due to a lack of comparative evidence, the decision to begin therapy, choice of therapy and duration should be based on patient preference, allergies, local resistance patterns, prior susceptibility, cost and side effects (Level 4 evidence, Grade C recommendation).

UTI: urinary tract infection; ACR: American College of Radiology.

**Postcoital antibiotics**

Postcoital antibiotic prophylaxis is another effective measure to prevent UTIs in women when sexual activity usually precedes UTI. Stapleton and colleagues conducted a randomized placebo-controlled trial with 16 patients in the treatment arm and 11 placebo to demonstrate an 0.3 CRPY in the treatment arm and 3.6 CRPY in the placebo.<sup>58</sup> A further randomized controlled trial found no difference in the efficacy of post-intercourse and daily oral ciprofloxacin with 70 patients in the post-intercourse and 65 in the daily group.<sup>48</sup> Additional uncontrolled trials have suggested equivalency of other antibiotic regimens.<sup>8</sup> Post-coital treatment involves taking a course of antibiotics within 2 hours of intercourse allowing for decreased cost and presumably side effects (Table 3).

**Self-start antibiotics**

Self-start antibiotic therapy is an additional option for women with the ability to recognize UTI symptomatically and start antibiotics.<sup>59-61</sup> Patients should be given prescriptions for a 3-day treatment dose of antibiotics. It is not necessary to culture the urine after UTI self-diagnosis since there is a 86% to 92% concordance between self-diagnosis and urine culture in an appropriately selected patient population.<sup>59-61</sup> Patients are advised to contact a health care provider if symptoms do not resolve within 48 hours for treatment based on culture and sensitivity.

## Other

## Estrogen

Vaginal estrogen may be an effective prophylaxis measure for UTI in postmenopausal women.<sup>62</sup> A 2007 Cochrane Database systematic review found two randomized studies which demonstrated a relative risk of symptomatic UTI during the study period of 0.25 (95% CI 0.13-0.50)<sup>63</sup> and 0.64 (95% CI 0.47-0.86)<sup>64</sup> favouring estrogen in both. Side effects include breast tenderness, vaginal bleeding or spotting, nonphysiologic discharge, vaginal irritation, burning and itching. Vaginal estrogen is also recommended by the SOGC for treatment of atrophic vaginitis and endometrial surveillance for this estrogen-associated cancer is felt to be unnecessary.<sup>65</sup> The type of vaginal estrogen is best determined by patient preference. Topical estrogen in the trial involved the use of 0.5 mg of estriol cream vaginally every night for 2 weeks, then twice a week for 8 months. The ring studied was Estring (Pharmacia and Upjohn), an estradiol-releasing ring changed every 12 weeks for a total of 36 weeks. Heterogeneity between studies did not allow a comparison of vaginal estrogens to antibiotics.

**Competing interests:** None declared.

This paper has been peer-reviewed.

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**Correspondence:** Dr. Anil Kapoor, Associate Professor of Surgery (Urology), McMaster University, Director, McMaster Urology Residency Program, 50 Charlton Av E, Hamilton, ON L8N 4A6; akapoor@mcmaster.ca