

# Recurrent Urinary Tract Infection in Women from a Urologist's Perspective

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## ABSTRACT

Urinary tract infection (UTI) referred to microbial invasion of the urinary tract system, typically due to bacteria. UTI is more common in women than men, which is thought to be due to differences in lower urinary tract anatomy. Making a diagnosis of UTI begins with the presence of clinical symptoms consistent with either pyelonephritis and cystitis. When pyelonephritis symptoms are present, it is usually associated with bacterial infection, while the symptoms of clinical cystitis may or may not be caused by infection. As both urologic and non-urologic conditions can produce the clinical symptoms of cystitis, diagnosis of UTI requires both pyuria and bacteriuria on urine examination. Complicated UTI is when the infection is associated with either host or bacterial factors that increase the chance of reinfection and decrease treatment efficacy, such as altered organism virulence, immunocompromise, or urinary tract abnormalities. The urologist's primary role in UTI management is to evaluate for such urinary tract abnormalities and, if needed, resolve those conditions to prevent recurrent infection. This review will describe the urologists' evaluation and management of complicated and recurrent UTI and inform physician about the urinary tract abnormalities that can predispose to recurrent UTI.

**Keywords:** Cystitis; urinary tract infection; urologic condition; investigation (Siriraj Med J 2023; 75: 55-61)

## INTRODUCTION

Urinary tract infection (UTI) is microbial invasion, typically bacterial, of the urinary tract. The global number of individuals with UTIs in 2019 is more than 404.6 million, with an incidence that is higher in women than in men.<sup>1</sup> In the United States, 10.8% of women self-reported that they had at least one presumed UTI during the past 12 months.<sup>2</sup> Several non-infectious genitourinary tract conditions can present with the same symptoms as UTI, so the diagnosis of UTI relies upon the combination of clinical symptoms consistent with pyelonephritis or cystitis accompanied by pyuria on urine analysis (UA) and significant bacteriuria on urine culture (UC). Importantly, in a small number

of cases, recurrent episodes may suggest the presence of factors that increase the chance of reinfection or decrease treatment efficacy, factors which distinguish uncomplicated from complicated UTI. Three main factors, including organism virulence, host immune system, and urinary tract abnormality, must be considered. To prevent reinfection, these factors need to be identified and properly treated. Collaboration among health care providers, especially infectious disease specialists and urologists are needed to cure patients with complicated UTI. From the urologist's perspective, a wide range of genitourinary tract conditions can present with the clinical syndromes of UTI; as these symptoms may or may not be associated with true bacterial infection, lack

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of complete evaluation can frequently result in delayed or missed diagnoses of underlying conditions. Therefore, this review would like to guide urologists in how to evaluate and diagnose complicated UTI, particularly in the context of genitourinary tract abnormalities, as well as inform physicians about preventive strategy for patients with uncorrectable conditions.

### How to diagnose UTI?

Basically, there are two clinical syndromes of UTI: pyelonephritis when the infection occurs in the upper urinary tract and cystitis for infection of the lower urinary tract. The symptoms of pyelonephritis are fever, flank pain, and/or chills, while the symptoms of cystitis are dysuria, frequency, urgency, urgency urinary incontinence, hematuria, and/or suprapubic pain. A meta-analysis examining the accuracy and precision of factors derived from the history and physical examination for UTI diagnosis in women showed that four symptoms: dysuria, frequency, hematuria, and back pain with costovertebral angle tenderness on exam significantly increased the probability of UTI. When dysuria and frequency were combined without vaginal discharge or irritation, the probability of UTI was greater than 90%.<sup>3</sup> However, while these clinical syndromes are most commonly linked to infections, non-infectious conditions, such as malignancy, may sometimes present with similar symptoms. To diagnose UTI correctly, urine examination including urine analysis (UA) and urine culture (UC) are essential. To be consistent with a diagnosis of UTI, UA should demonstrate pyuria, defined as the presence of  $\geq 3$  white blood cells per high power field of unspun urine or  $\geq 10$  white blood cell per cubic millimeter<sup>4</sup> and significant bacteriuria. Pyuria without bacteriuria, termed sterile pyuria, may indicate urologic malignancy, urolithiasis, or genitourinary tract tuberculosis. It is also important to note that the presence of bacteriuria on UA is not always indicative of an infection. Both colonization and contamination can present with significant bacteriuria, so symptoms are an important component of the diagnosis of UTI.

Urine culture (UC) is still considered the gold standard investigation for diagnosis of bacterial UTI; but there is substantial debate about the appropriate threshold of colony forming units (CFU) count. Previously, a cut-off value of  $10^5$  CFU/ml was widely accepted as significant bacteriuria consistent with infection. However, in patients with convincing signs and symptoms of infection, a lower threshold of  $10^2$  CFU/ml is reasonable.<sup>5</sup> In addition, standard clinical urine culture does not detect all bacteria equally, preferentially detecting aerobic

bacteria. If anaerobic bacterial or mycobacterial infections are suspected, special staining, culture techniques, or molecular diagnostic approaches, such as polymerase chain reaction (PCR), may be required.

In summary, a diagnosis of UTI requires the combination of the constellation of symptoms seen in UTI clinical syndromes and abnormal urine testing demonstrating pyuria and significant bacteriuria.

### What is complicated UTI?

To determine appropriate management, UTI should be divided into uncomplicated and complicated subtypes. Complicated UTI is defined as infections associated with factors that increase the chance of reinfection and/or decrease treatment efficacy, such as atypical, highly virulent or drug-resistant organisms, host immune dysregulation, and urinary tract abnormalities.<sup>5</sup> The management of complicated UTI requires thorough evaluation and management of any correctable factors to break the cycle of recurrence.

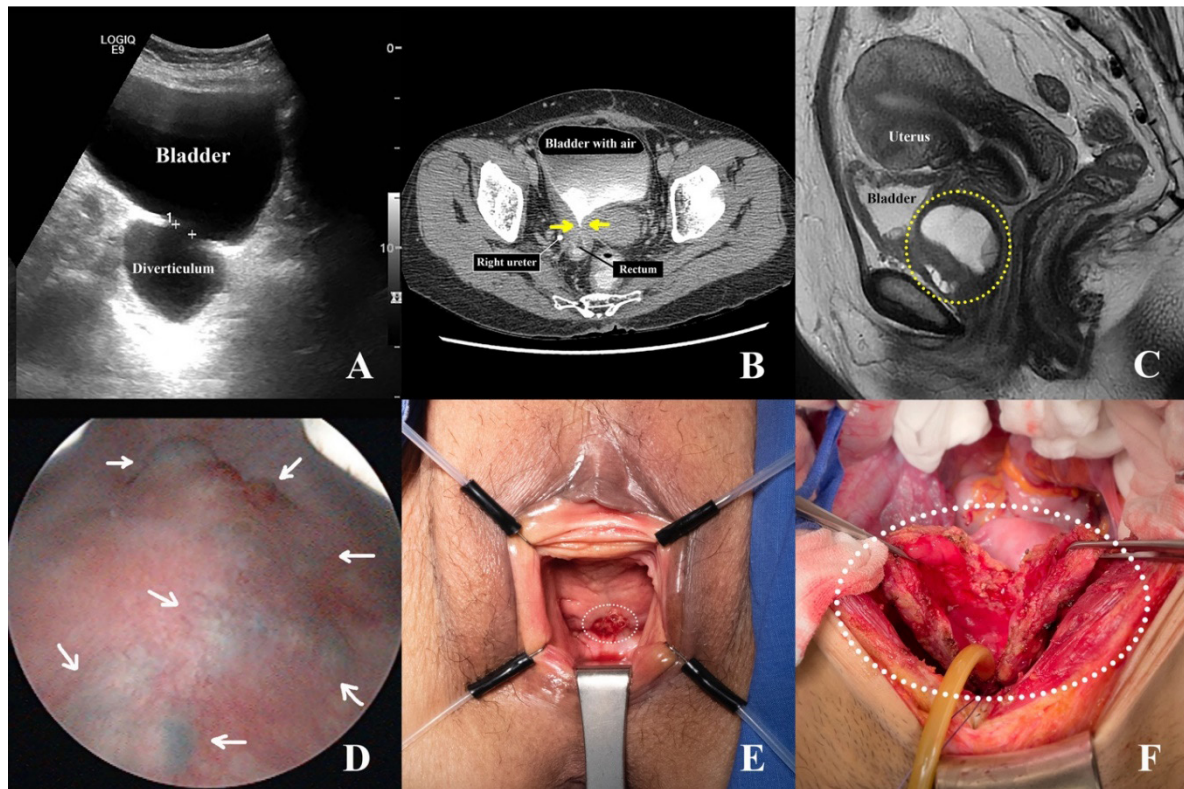
Recurrent UTI is defined as  $\geq 2$  episodes within 6 months or  $\geq 3$  episodes of within 12 months of microbiologically diagnosed UTI. With these infections, symptoms should resolve between episodes prior to diagnosis of another UTI.<sup>5,6</sup> Risk factors for recurrent UTIs differ between age groups. In women age less than 40 years of age, risk factors typically relate to sexual behavior and spermicide use.<sup>7-9</sup> In postmenopausal women, a history of previous UTIs, prior urogenital surgery, symptomatic urinary incontinence, presence of cystocele on vaginal examination, maximal urine flow  $\leq 15$  ml/sec defined by uroflowmetry, and elevated post-void residuals were associated with a higher risk of recurrent UTI.<sup>10</sup> Therefore, there is a higher likelihood of functional and anatomic urinary tract abnormalities in this older population, which necessitates thorough investigation.

### Conditions associated with clinical cystitis

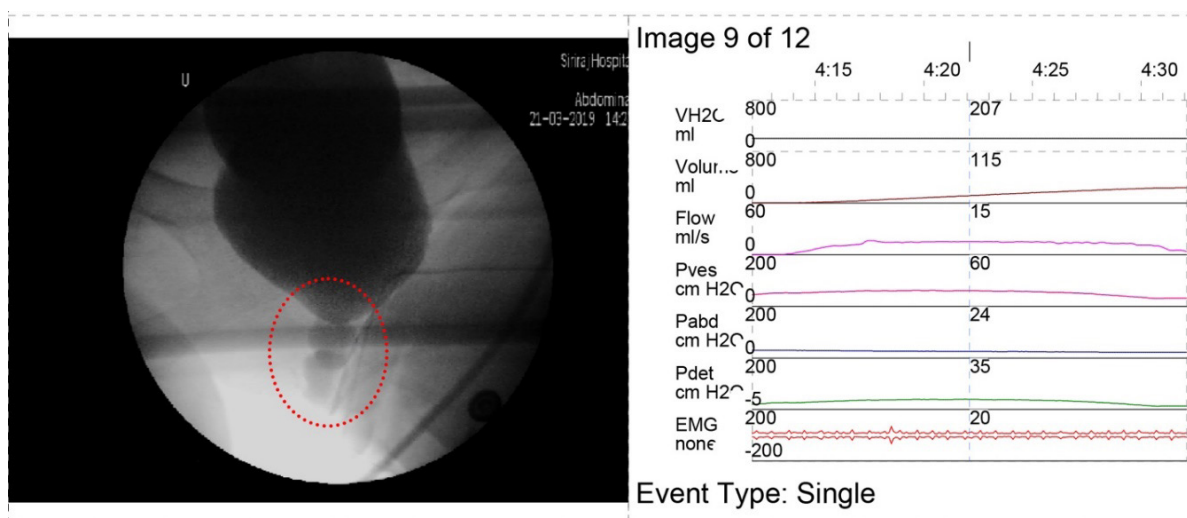
Most episodes of clinical pyelonephritis are bacterial infections, which typically requires hospital admission for evaluation and treatment. In contrast, the clinical syndrome of cystitis is typically managed in the outpatient setting, and thus is not always thoroughly evaluated. Multiple urologic and non-urologic conditions with or without simultaneous bacterial infection can cause recurrent clinical cystitis symptoms. In addition to uncomplicated cystitis, other urologic conditions, such as malignancy, urolithiasis, neurogenic lower urinary tract dysfunction, tuberculosis of urinary tract, ketamine-induced cystitis, radiation-induced cystitis, interstitial cystitis, bladder diverticulum, urethral diverticulum, urethral stricture,

periurethral fibrosis, and functional bladder outlet obstruction, can cause cystitis-like symptoms. Non-urologic conditions can be of a gynecologic (e.g., pelvic organ prolapse, endometriosis, and uterine/cervical/vaginal tumor) or colorectal (colovesical fistula, diverticulitis, and rectal tumor) origin. (Fig 1 & 2) Other rare conditions

causing clinical symptoms of cystitis are pelvic congestion syndrome and non-relaxing pelvic floor dysfunction. All conditions can initially be evaluated with careful history and physical examination. If needed, additional investigations can be considered to confirm the suspected diagnosis.



**Fig 1.** (A) Ultrasonography demonstrates a bladder diverticulum, an outpouching lesion arising from the posterior bladder wall. (B) Computed tomography demonstrates a rectovesical fistula, occurring after low anterior resection for rectal cancer. (Yellow arrows) (C) Magnetic resonance imaging shows a urethral diverticulum, an outpouching lesion arising from and wrapping around the urethra. (Yellow circle) (D) Cystoscopy demonstrated endometriosis, involved posterior bladder wall, seen as tortuous dark-blue lesions. (White arrows) (E) Vaginal examination demonstrated mesh extrusion (white circle) after pelvic organ prolapse repair, causing of vaginal infection and clinical cystitis-like symptoms. (F) Intraoperative findings from abdominal cystostomy demonstrated a severely contracted and inflamed bladder wall (white circle) from ketamine abuse.



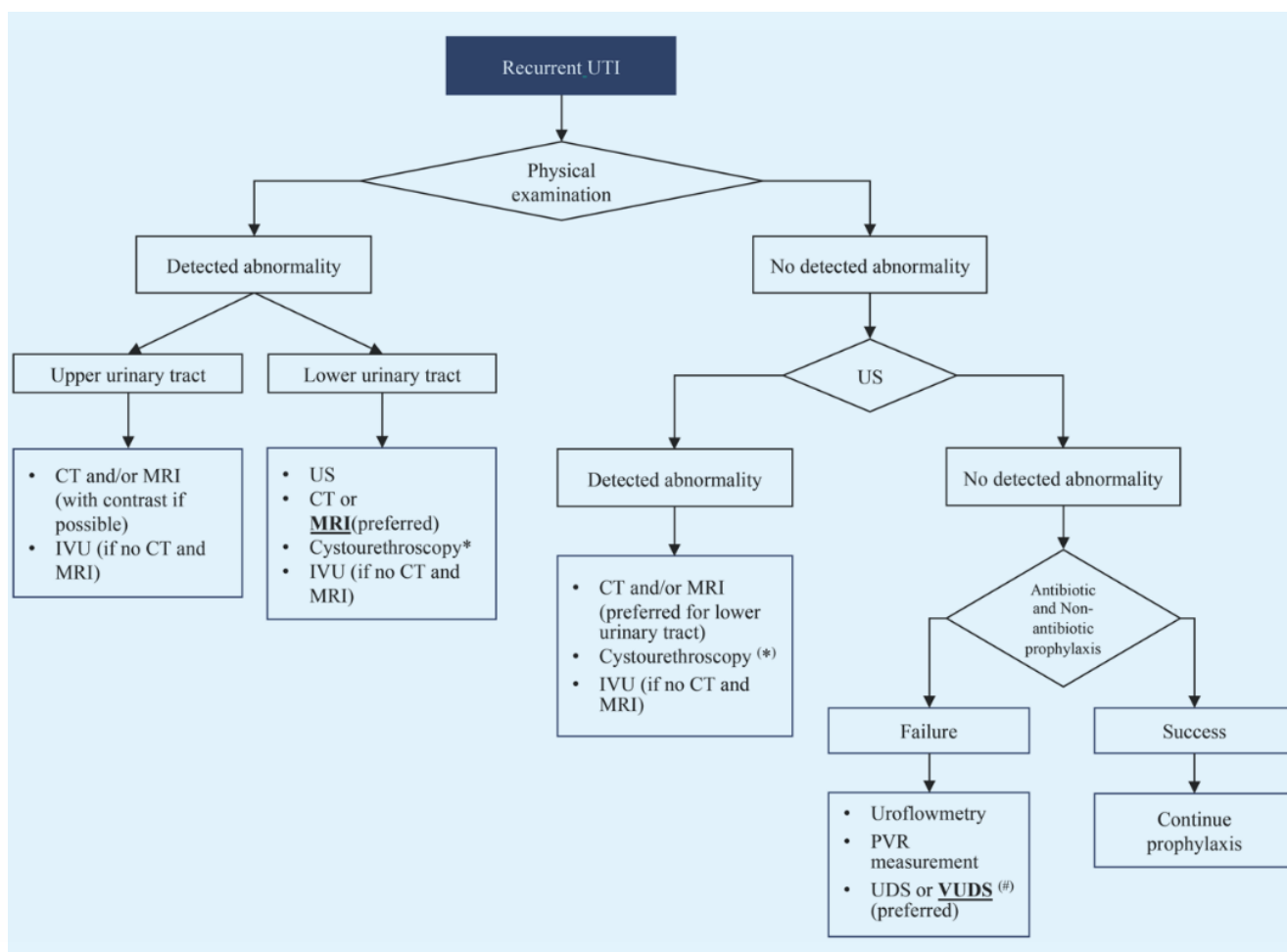
**Fig 2.** Voiding cystourethrography with concomitant intravesical pressure measurement on videourodynamics demonstrated urethral distortion (Red circle) and high detrusor contraction with low urine flow (Graph) consistent with bladder outlet obstruction after anterior vaginal wall repair.

### Investigation for recurrent UTIs

Generally, anatomical evaluation for urinary tract abnormalities can include ultrasonography (US), intravenous urography (IVU), computed tomography (CT), and magnetic resonance imaging (MRI). Multiple studies, however, have shown little benefit for routine anatomical investigation in women with recurrent UTI.<sup>11,12</sup> IVU is rarely helpful; more than 80% of IVU in women with recurrent UTIs are completely normal.<sup>13-15</sup> As an initial investigation in women in whom there is suspicion of anatomic abnormalities, US is recommended as an initial investigation to replace IVU; US is inexpensive, non-invasive, confers no radiation exposure, and can provide guidance for further investigations.<sup>16</sup> CT and MRI are not routinely performed and only recommended in cases in which specific conditions, such as colovesical fistula, are suspected or abnormalities were previously detected on physical examination or US. Cystoscopy rarely provides any information that would alter management; the most common finding is mucosal inflammation.<sup>12,14,17</sup>

If no abnormal findings are seen on US or CT, 94% of subsequent cystoscopies are normal.<sup>17</sup> Therefore, cystoscopy is only considered in specific conditions, such as hematuria, suspected malignancy, or suspicion for other specific clinical condition.

If anatomic investigation fails to demonstrate an abnormality, it is reasonable to consider functional investigation of the lower urinary tract.<sup>12,18</sup> Investigation can include non-invasive uroflowmetry (UFM), assessment of post-void residual urine (PVR), and urodynamic (UDS) assessment with or without video assessment (VUDS). In principle, functional abnormalities should be focused on incomplete bladder emptying and voiding dysfunction. VUDS showed evidence of lower urinary tract dysfunction in 67 – 90% in women with recurrent UTIs.<sup>18,19</sup> The most common finding was bladder outlet dysfunctions in 63% of women, with a hypocontractile detrusor seen in 16%.<sup>19</sup> Together, this evidence suggests an algorithmic investigation of women with recurrent UTI. (Fig 3)



(\*) Cystourethroscopy when US, CT or MRI demonstrates lower urinary tract abnormality or history of lower urinary tract surgery.

(#) UDS or VUDS is indicated when uroflowmetry shows abnormality or PVR measurement is more than 20% of bladder capacity.

**Fig 3.** Proposed investigation flow for women with recurrent UTI



### Reasons of treatment failure in urinary tract abnormality

UTIs can continue to recur due to antimicrobial resistance, biofilm formation, and immunocompromise in the host, as well as the anatomical and functional abnormalities discussed above. When the underlying cause is clearly diagnosed and appropriately treated either with surgery or medication, UTI can often be cured without recurrences. Unfortunately, majority of cases are combined between both abnormalities. Even after correcting an anatomical abnormality, UTI can still recur, frequently because of a previously co-existing or new-onset functional abnormality. Such new-onset ("de novo") abnormalities may or may not be associated with the surgical repair. It is important to consider re-evaluation if UTIs continue to recur after anatomical correction, although this should only proceed after an appropriate interval for healing to avoid confounding factors occurring after surgery. Occasionally, it is not possible to correct the urinary tract abnormalities and continuous preventive strategies are necessary.

### Prevention for recurrent UTIs

Prevention strategies aim to decrease UTI episodes in patients waiting for definitive treatment, those with uncorrectable conditions who have little chance of complete bacterial eradication, or those who are unable or unfit for surgical correction of their underlying condition. Strategies include antibiotic and non-antibiotic prophylaxis regimens.

Antibiotic prophylaxis regimens including continuous low-dose and post-coital antibiotics. One systematic review indicated that continuous antibiotic prophylaxis for 6 – 12 months could significantly reduce the rates of UTI in comparison to placebo.<sup>20</sup> Post-coital antibiotics are a reasonable option for prevention in patients whose cases of UTI are associated with sexual intercourse.<sup>20</sup> While continuous antibiotic prophylaxis can prevent recurrent episodes, however, this regimen potentially increases urinary and fecal antibiotic resistance. In addition, infections tend to recur once the antibiotics are stopped.<sup>21</sup> Given these limitations, there are many agents to use for non-antibiotic prophylaxis, including probiotics, estrogen, urine acidification agents, cranberries, and D-mannose.

### Probiotics

Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) defines probiotics as live microorganisms which, when administered in adequate amounts, confer a health benefit to the host.<sup>22</sup> The most common probiotic

used for preventing UTI in women is *Lactobacillus*. A randomized, double-blinded, non-inferiority trial comparing antibiotic prophylaxis with 480 mg of trimethoprim-sulfamethoxazole once daily to oral capsules containing *Lactobacilli* twice daily for 12 months demonstrated that *Lactobacilli* were not inferior to antibiotic prophylaxis in the prevention of UTI. Moreover, *Lactobacilli* did not increase antibiotic resistance.<sup>23</sup> However, given only a small number of equivocal studies, a lack of consistent probiotic formulations, and a high risk of bias, a recent systematic review and meta-analysis study concluded there was insufficient evidence to determine the benefit of probiotics for UTI.<sup>24</sup>

### Estrogen

Lack of estrogen in postmenopausal women may contribute to a risk of recurrent UTI because the changing vaginal environment. Loss of the normal flora may allow pathogens to colonize and infect the lower urinary tract. A systematic review and meta-analysis showed that while oral estrogen did not significantly reduce the number of women with UTI in comparison to placebo, vaginal estrogen use significantly reduced the number of UTI when compared to both placebo and no treatment.<sup>25</sup> Reported adverse events were rare, but include breast tenderness, vaginal bleeding or spotting, vaginal discharge, and vaginal irritation or burning.<sup>25</sup> While typical vaginal estrogen doses are associated with little systemic absorption, treatment with estrogen must be used with caution in endometrial cancer, breast cancer, cardiovascular disease, deep venous thrombosis, pulmonary embolism and chronic liver disease.

### Urine acidification agents

Bacterial growth is inhibited by acidified urine, so agents which can reduce urine pH may be effective treatments. Commonly used agents are Methenamine Hippurate and ascorbic acid. While the concept of urinary acidification has promoted the use of ascorbic acid, known as vitamin C, for UTI prevention, there is no strong evidence to support its use in prevention of recurrent UTI. Methenamine hippurate will also acidify the urine and has an additional bacteriostatic effect due to its peripheral metabolism into formaldehyde in the urinary tract. Dosage ranges between 1 and 4 g daily. Common adverse events are gastrointestinal irritation, abdominal cramps, anorexia, rash, stomatitis, and dysuria. While previous data had suggested a small benefit in patients without urinary tract abnormalities, a systematic review and meta-analysis demonstrated that the overall quality of the previous studies was poor, often

examining heterogenous populations.<sup>26</sup> As a result, this agent had not been recommended in any guidelines. A recent, randomized clinical trial, however, demonstrated non-inferiority of methenamine to continuous antibiotic prophylaxis in the prevention of recurrent UTI, suggesting this agent may have utility in UTI prophylaxis.<sup>27</sup>

### Cranberries

A-type proanthocyanidins (PACs), found in high levels in cranberries, can prevent bacterial adhesion.<sup>28</sup> As a result, cranberries have been suggested as non-antibiotic prophylaxis for UTI because many studies had demonstrated that it can prevent bacterial adhesion to the urothelium in vitro.<sup>29,30</sup> Focusing on the outcome of women with recurrent UTI in systematic review and meta-analysis study, a meta-analysis of four studies comparing between cranberry and placebo or no treatment showed a small, non-significant reduction in risk of repeat symptomatic UTI but the analysis of two studies comparing cranberry product and antibiotic prophylaxis showed equally effective.<sup>31</sup> Importantly, cranberry tablets may alter urinary oxalate and uric acid excretion, so patients with a history of urolithiasis should be counselled about this risk before choosing cranberry as a preventative approach.<sup>32</sup> Until now, the evidence to support a role of cranberries for UTI prevention is inconclusive. Recent evidence, however, suggests that some of the conflicting evidence regarding cranberry efficacy in UTI prevention may come from differences in cranberry formulations and products; varying amounts of bioactive PACs within each product may underlie differing efficacies in UTI prevention.<sup>33,34</sup> As no serious adverse events have been reported, cranberries may be used in patients who desire a non-antibiotic approach.

### D-mannose

D-mannose, a type of sugar, prevents bacterial adhesion to the urothelium both in vitro and in animal studies by binding to bacterial pili.<sup>35,36</sup> For clinical use, a recent meta-analysis of two randomized controlled trials and one prospective study showed that D-mannose treatment had similar effectiveness in preventing subsequent UTIs as antibiotic prophylaxis with minimal adverse events, but the studies were again of poor to fair quality due to allocation concealment and lack of blinding. Dosage was various from 420 to 6,000 mg daily, varying significantly between studies and formulations used. Adverse events, such as diarrhea and gastrointestinal irritation, were typically mild.<sup>37</sup>

## CONCLUSION

Urinary tract infection (UTI) is a common problem in women. Many urologic and non-urologic conditions may present with the same clinical syndrome as UTI, including pyelonephritis and cystitis. Therefore, urine examination including urine analysis and culture is critical to confirm infection. In addition, some of these non-infectious conditions can confer an increased risk of recurrent UTI; therefore, in cases in which an anatomic abnormality is suspected from history and physical examination or recurrent episodes are refractory to treatment, further investigation should be considered. In cases of complicated UTI that are unable to be cured by definitive treatment, preventive strategies should be employed to decrease UTI episodes and prevent further consequences.

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