

# Evaluating suppressive therapies to prevent recurrent urinary tract infections: A literature review

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Because of increased antibiotic resistance rates, healthcare providers need to determine the usefulness of non-antibiotic suppressive therapies for women experiencing recurrent urinary tract infections (UTIs). The authors reviewed the literature to ascertain which, if any, of these non-antibiotic suppressive therapies might be effective in preventing recurrent UTIs in women.

**KEY WORDS:** urinary tract infection, UTI, prophylaxis, prevention, recurrence, antibiotics

**R**ecurrent bacterial urinary tract infections (UTIs) are common in women; symptoms vary in severity from minor to life threatening. UTIs not only affect quality of life but also have a vast financial impact, accounting for more than \$2.6 billion in healthcare costs annually in the United States.<sup>1</sup> Eells et al<sup>2</sup> reported that 20%-30% of women presenting to clinic with a UTI go on to experience a second UTI within 6 months. UTIs lead to more than 470,000 hospitalizations each year.<sup>2</sup> More than 50% of U.S. women experience a UTI at least once in their lifetime.<sup>1-3</sup> Risk factors for UTI include elevated residuals due to pelvic floor dysfunction, decreased fluid intake, low estrogen levels, sexual intercourse, and anatomic abnormalities.<sup>4</sup> Osamwonyi and Foley<sup>4</sup> reported an average yearly recurrence rate of 2.6 infections after initial infection.

By definition, recurrent UTIs, diagnosed by urine culture, are two episodes in a 6-month period or three episodes in 1 year.<sup>5-11</sup> Re-infection is most often due to a different pathogen after initial successful treatment and should not be confused



with relapse.<sup>12</sup> Typical symptoms of UTI, recurrent or otherwise, include dysuria, increased urinary frequency, urinary urgency, and hematuria.<sup>13</sup>

Both antimicrobial and non-antimicrobial agents, as well as behavioral therapies, have been used for suppressive therapy in patients with recurrent UTIs. In particular, suppressive therapeutic interventions include increased fluid intake; low-dose antibiotics; D-mannose; cranberry products, including juice, extract, and tablets; probiotics; intravesical treatments; vaccines; and vaginal estrogen.<sup>4,12,13</sup> The American Urological Association recommends low-dose antibiotics as the first-line approach for recurrent UTI prophylaxis.<sup>14</sup> By contrast, the European Association of Urology guidelines for prophylaxis suggest starting with behavioral changes, followed by non-antimicrobial therapy, and, finally, antimicrobials.<sup>13</sup> Non-antimicrobial treatments are gaining popularity in this country as healthcare providers (HCPs) and women alike seek out alternatives to antibiotics.

## Literature review

Because of increased antibiotic resistance rates, HCPs need to consider the efficacy of other suppressive therapies for recurrent UTIs. The purpose of this literature review was to assess current evidence regarding the efficacy of suppressive therapies in preventing recurrent UTIs in women.

## Methods

### **Search engines, key terms, and initial article yield**

A comprehensive search of three databases was performed through a university library. Databases searched included PubMed, Embase, and Scopus. Key terms used to locate applicable information were *recurrent urinary tract infection* and *prevention*. The initial search yielded a total of 1,903 results: 683 articles

# Non-antibiotic treatments have been shown to have variable efficacy in preventing recurrent UTIs.

from Embase, 329 articles from PubMed, and 891 from Scopus.

### **Inclusion and exclusion criteria and final article yield**

Following the initial search, inclusion criteria limited articles to those (1) published in the past 5 years, (2) pertaining to females only, and (3) written in English. All articles were obtained in full text from the initial search. After application of these criteria, 63 Embase articles, 31 PubMed articles, and 95 Scopus articles remained. Systematic reviews, meta-analyses, literature reviews, and ongoing clinical trials were excluded. Articles with a specific focus on postsurgical patients, pediatric patients, kidney disease, pelvic floor prolapse, and pregnant women were also excluded, along with duplicate articles and those not applicable to the subject of this literature review. Upon application of exclusion criteria, eight articles remained. These articles were reviewed judiciously to ensure relevance to prevention of recurrent UTIs in women and to determine level of evidence. The eight studies described in these articles met criteria for Level II evidence based on the Fineout-Overholt paradigm.<sup>15</sup>

### **Synthesis of evidence**

Seven of the articles defined recurrent UTIs as three or more infections in 1 year;<sup>5-11</sup> one article considered two UTIs in a 1-year pe-

riod to be recurrent.<sup>16</sup> The articles described a variety of suppressive therapies to prevent recurrent UTIs in women (*Table*). Suppressive therapies studied included antibiotics,<sup>6-10</sup> intravesical treatments,<sup>5,7</sup> lactobacilli,<sup>6</sup> D-mannose,<sup>8,10</sup> a sublingual vaccine,<sup>9</sup> an oral hyaluronic acid (HA)/chondroitin sulfate (CS) combination,<sup>11</sup> vaginal estrogens,<sup>11</sup> and a cranberry product.<sup>16</sup>

## Results

The literature review yielded three themes: (1) long-term suppressive therapy with low-dose antibiotics was not nearly as effective as perceived to be; (2) efficacy of non-antibiotic suppressive treatment options for recurrent UTIs varied; and (3) providers sought out non-antibiotic therapies for suppression for a multitude of reasons.

### **Efficacy of long-term use of low-dose antibiotics**

For years, long-term use of low-dose antibiotics has been the suppressive approach of choice for recurrent UTIs. Because of increased drug resistance, these antibiotics are not as effective as they once were, and women are experiencing recurrences.<sup>5,7,9,10</sup> Beerepoot et al<sup>6</sup> conducted a randomized, double-blind, noninferiority trial of trimethoprim-sulfamethoxazole (TMP/SMX) versus lactobacilli in preventing recurrent UTI in 252 postmenopausal women. TMP/SMX and lactobacilli therapies did not differ

significantly in preventing recurrent UTIs over 1 year. However, after 1 month of TMP/SMX prophylaxis, resistance to TMP/SMX, TMP, and amoxicillin had increased from 20%-40% to 80%-95% among *Escherichia coli* from the feces and urine of asymptomatic women and among *E. coli* causing a UTI. Resistance did not increase during lactobacilli prophylaxis. In other studies, TMP/SMX was found less effective for chronic suppression when compared with oral D-mannose or Uromune, a sublingual therapeutic vaccine available in Spain.<sup>9,10</sup>

### Variable efficacy of non-antibiotic suppressive treatments

Non-antibiotic treatments have

been shown to have variable efficacy in preventing recurrent UTIs. These treatments have differing mechanisms of action, as follows:

- **Glycosaminoglycan (GAG)-strengthening properties.** Evidence suggests that a defect in the protective GAG layer of the urothelium contributes to recurrent UTIs.<sup>5,7,11</sup> In three separate studies, women receiving intravesical heparin, intravesical HA/CS, or oral HA/CS plus curcumin and quercetin experienced a decreased number of recurrences over a 6- to 12-month period because of these therapies' GAG-strengthening properties.<sup>5,7,11</sup>

- **Provision of a vehicle (other than the epithelium) to which bacteria can adhere.** Two studies showed that, with long-term use, D-mannose provided a vehicle to which UTI-causing bacteria could adhere (as opposed to the epithelium).<sup>8,10</sup>
- **Inhibition of adhesion.** In one study, cranberry fruit powder containing high levels of proanthocyanidins (500 mg), as compared with placebo, led to a 58% relative risk reduction in recurrent UTIs over a 6-month period.<sup>16</sup>
- **Provision of immunity against multiple strains of UTI-causing pathogens.** A multicenter observational study showed that the Uromune sublingual vac-

**Table.** Studies assessing use of suppressive therapies to prevent recurrent urinary tract infections

Study	Purpose	Study design/sample	Results	Conclusion
Above et al, 2013 <sup>5</sup>	To assess the effect of bladder instillations of heparin on the rate of UTIs in women resistant to standard therapy	In this pilot study, 18 women (mean age, 67 y) with a history of recurrent UTI received intravesical instillations of heparin 40,000 U, 2% lidocaine 8 mL, and sodium bicarbonate 4 mL once weekly for 6 weeks.	78% of patients responded to therapy.	Bladder instillations of heparin decreased the UTI rate.
Beerepoot et al, 2012 <sup>6</sup>	To assess efficacy of lactobacilli as prophylaxis for recurrent UTIs in women compared with single-strength TMP/SMX	In this randomized double-blind noninferiority trial, 252 postmenopausal women with recurrent UTI received 12 months of prophylaxis with TMP/SMX 480 mg/d or oral capsules containing 109 colony-forming units of <i>Lactobacillus rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 BID.	Between-treatment difference of 0.4 UTIs/y was outside the noninferiority margin. Median time to first UTI was 6 months in the TMP/SMX group and 3 months in lactobacilli group. After 1 month of TMP/SMX use, resistance to TMP, TMP/SMX, and amoxicillin increased from 20%-40% to 80%-95% in <i>Escherichia coli</i> from the feces and urine of asymptomatic women.	<i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-1, compared with TMP/SMX, did not meet noninferiority criteria in the prevention of UTIs. Unlike TMP/SMX, lactobacilli did not increase antibiotic resistance.
De Vita & Giordano, 2012 <sup>7</sup>	To evaluate the effect of intravesical HA/CS in recurrent bacterial cystitis	In this randomized study, 28 women received intravesical HA 800 mg and CS 1 g in 50 mL of saline solution once weekly for 4 weeks, then once every 2 weeks for 2 more weeks, or TMP/SMX 40 mg/200 mg orally once weekly for 6 weeks.	26 of 28 women completed follow-up. The HA/CS group, compared with the TMP/SMX group, showed significant improvement over 12 months, with fewer cystitis recurrences (1 ±1.2 vs 2.3±1.4).	Compared with oral antibiotic prophylaxis, intravesical HA/CS significantly reduced bacterial cystitis recurrence and improved quality of life, urinary symptoms, and cystometric capacity at 12-month follow-up.
Kranjcec, et al, 2014 <sup>8</sup>	To test whether D-mannose powder is effective for recurrent UTI prevention	After initial antibiotic treatment, 308 women with a history of recurrent UTI were randomly assigned to one of three groups. Group 1 (n = 103) received 2 g of D-mannose powder in 200 mL of water daily for 6 months. Group 2 (n = 103) received nitrofurantoin 50 mg/d for 6 months. Group 3 (n = 102) did not receive prophylaxis.	98 patients had recurrent UTI: 15 (14.6%) in the D-mannose group, 21 (20.4%) in the nitrofurantoin group, and 62 (60.8%) in the no prophylaxis group.	D-mannose powder significantly reduced risk of recurrent UTI, as did nitrofurantoin. Initial findings show D-mannose may be useful for UTI prevention.

ET, estrogen therapy; HA/CS, hyaluronic acid/chondroitin sulfate; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

cine containing an inactivated bacterial cell suspension of selected strains of *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *E. faecalis* led to a 75% improvement in recurrence rate in the first 3 months and a 77% improvement at the 15-month mark.<sup>9</sup> This treatment was significantly superior to TMP/SMX in reducing UTI recurrences.

- **Interference with the adherence, growth, and colonization of uropathogenic bacteria.** Although the efficacy of oral lactobacilli versus TMP/SMX did not differ significantly in terms of preventing UTI recurrence, as mentioned previously, a decrease in the

incidence of antibiotic resistance was demonstrated in lactobacilli users.<sup>6</sup>

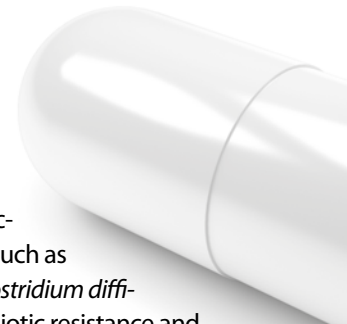
### Reasons for selection of non-antibiotic therapies

All of the articles indicated that researchers are investigating other options for suppressive therapy—largely because of concerns about widespread antibiotic resistance. Heterogeneous, uropathogenic *E. coli* strains are the cause of more than 80% of uncomplicated UTIs,<sup>17</sup> and resistance of *E. coli* to antibiotics is increasing.<sup>7</sup> In fact, Lorenz-Gomez et al<sup>9</sup> reported that in some geographic locations throughout the world, more than 40% of bacterial strains are resistant

to antibiotics.

In addition, the use of antibiotics to treat recurrent UTIs can lead to secondary infections such as candidiasis and *Clostridium difficile* infection. Antibiotic resistance and adverse reactions likely contribute to the annual billions of dollars in health-care costs related to UTIs.<sup>5,8,9</sup> Today, traditional suppressive therapy with antibiotics may be both ineffective and costly in many cases.

Beyond concerns about efficacy, patients complain about the side effects associated with long-term antibiotic use, leading them to discontinue treatment. In all of the



**Table.** Studies assessing use of suppressive therapies to prevent recurrent urinary tract infections

Study	Purpose	Study design/sample	Results	Conclusion
Lorenz-Gomez et al, 2013 <sup>9</sup>	To evaluate the use of the sublingual bacterial vaccine Uromune to prevent recurrent UTIs	In this multicenter observational study, the clinical histories of 319 women who presented with $\geq 2$ episodes of UTI in the past 6 months or 3 UTIs in 12 months were reviewed. A total of 159 patients received Uromune daily for 3 months and 160 patients received TMP/SMX 40/200 mg/d for 6 months.	In the first 3 months, the mean number of UTIs was 0.36 in the Uromune group vs 1.6 in the TMP/SMX group. Respective numbers of patients with no UTI at 3, 9, and 15 months were 101, 90, and 55 in Uromune group vs 9, 4, and 0 in the TMP/SMX group.	Results in this study favor the use of Uromune as an effective strategy to reduce frequency, duration, severity, and cost of recurrent UTIs.
Porru et al, 2014 <sup>10</sup>	To evaluate the efficacy of D-mannose in the treatment and prophylaxis of recurrent UTI	In this randomized crossover trial, 60 women who had an acute symptomatic UTI and $\geq 3$ recurrent UTIs during the preceding 12 months were randomized to TMP/SMX 160/800 mg or oral D-mannose 1 g TID for 2 weeks and then 1 g BID for 22 weeks. They received the other intervention in the second phase of the study, with the primary endpoint of elapsed time to recurrence.	Mean time to recurrence was 52.7 days with antibiotic treatment and 200 days with oral D-mannose.	D-mannose appeared to be a safe and effective treatment for recurrent UTI in women. A significantly greater proportion of D-mannose recipients than TMP/SMX recipients remained UTI free.
Torella et al, 2016 <sup>11</sup>	To assess whether oral HA/CS, curcumin, and quercetin could be effective in preventing recurrent cystitis in postmenopausal women and whether efficacy might be affected by concurrent use of local ET	In this prospective evaluation, 145 postmenopausal women with mild to moderate urogenital atrophy and a history of recurrent UTI within the preceding 12 months were consecutively recruited from the database of three different investigators. Group 1 was treated with vaginal ET; group 2 with oral HA/CS, curcumin, and quercetin; and group 3 with both.	Respective proportions of women with $< 2$ infective episodes at 6 months were 8%, 11.1%, and 25% in groups 1, 2, and 3. At 1 year, the proportion of women with $< 3$ infective episodes was almost double in group 3 vs groups 1 and 2, although improvement was significant in all 3 groups.	In postmenopausal women, the combination of oral HA/CS, curcumin, and quercetin was effective in preventing recurrent UTIs, especially if administered with vaginal ET.
Vostalova et al, 2015 <sup>16</sup>	To assess whether whole cranberry fruit powder (proanthocyanidin content 0.56%) could prevent recurrent UTI in women with $\geq 2$ UTI episodes in the preceding year.	Participants were randomized to cranberry powder 500 mg/d ( $n = 89$ ) or placebo ( $n = 93$ ) for 6 months.	Intent-to-treat analysis showed that in the cranberry group, UTIs were significantly fewer (10.8% vs 25.8%, with an age-standardized 12-month UTI history. Kaplan-Meier survival curves showed that the cranberry group experienced a longer time to first UTI than the placebo group.	Cranberry fruit powder (peel, seeds, pulp) may reduce the risk of symptomatic UTI in women with a history of recurrent UTIs.



# Awareness of the efficacy of available options for suppression of UTI recurrence allows HCPs to implement evidence-based care in clinical practice.

articles reviewed, no adverse side effects were reported with any of the non-antibiotic prophylactic interventions. Furthermore, many women state a preference for avoiding antibiotic use and actively seek alternative options.<sup>6,7</sup>

## Discussion

The purpose of this literature review was to explore current evidence regarding effective suppressive therapies to prevent recurrent UTIs in women. Researchers for the eight studies discussed in this article explored the potential of non-antibiotic suppressive therapies, alone or in combination with long-term antibiotic use, for prevention of recurrent UTIs. The scope of studies reviewed was limited to those available in full-text format. However, the articles chosen represent the varied therapies currently in use and/or being studied.

Seven of the studies were conducted in Europe. In fact, European guidelines represent a shift toward using behavioral and non-antibiotic therapies *first* to prevent UTI recurrence, resorting to antibiotics only when other therapies are not effective.<sup>13</sup> However,

no standard evidence-based guidelines are available for providing non-antibiotic options for treatment. Long-term low-dose antibiotic use is still considered first-line therapy in the U.S., although this approach is recognized as not as effective as it once was because of growing antibiotic resistance.

The short- and long-term efficacy of non-antibiotic options needs further study. More studies are needed to investigate the efficacy of combination therapy, including prophylactic long-term antibiotics plus non-antibiotic therapies and different combinations of non-antibiotic therapies (i.e., without any antibiotics). Approval for a vaccine in the U.S. has the potential to reduce the need for antibiotic prophylaxis or other non-antibiotic therapies. Effective multi-strain vaccines are currently available in Europe for prevention of UTI recurrence.<sup>9,19</sup> As knowledge expands with ongoing research, the data may well support new guidelines for the prevention of recurrent UTIs.

## Implications for practice

Awareness of the efficacy of available options for suppression of UTI recurrence allows HCPs to implement evidence-based care in clinical practice. Choosing non-antibiotic suppressive therapies shown to be effective, as opposed to low-dose antibiotics, as first-line treatment is

reasonable, especially with increasing resistance rates. HCPs should discuss all available options with women so that informed treatment decision-making meets individual patient needs and preferences.

## Conclusion

Treatment of recurrent UTIs is a challenge. The studies reviewed in this article illustrate an international interest in finding safe, effective, acceptable therapies beyond the use of antibiotics. The data indicate a need for more research. A goal is to have the information needed to develop evidence-based guidelines for prevention of UTI recurrence that allow for individualized care and better outcomes. ●

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## References

1. Suskind AM, Saigal CS, Hanley JM, et al. Incidence and management of uncomplicated recurrent urinary tract infections in a national sample of women in the United States. *Urology*. 2016;90:50-55.
2. Eells S, Bharadwa K, McKinnell J, et al. Recurrent urinary tract infections among women: comparative effectiveness of 5 prevention and management strategies using a Markov chain Monte Carlo model. *Clin Infect Dis*. 2014;58(2):147-160.
3. Burleigh AE, Benck SM, McAhern SE, et al. Consumption of sweetened, dried cranberries may reduce urinary tract infection incidence in susceptible women – A  
(continued on page 43)



2017;40(suppl 1):S1-S132.

12. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007;30(suppl 2):S251-S260.
13. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773.
14. National Diabetes Data Group Classification. and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28:1039-1057.
15. National Institutes of Health consensus development conference statement: diagnosing gestational diabetes mellitus, March 4-6, 2013. *Obstet Gynecol*. 2013;122(2 pt 1):358-369.
16. World Health Organization (WHO). *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Geneva, Switzerland: Author; 2013.
17. Hernandez TL, Van Pelt RE, Anderson MA, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. *Diabetes Care*. 2014;37(5):1254-1262.
18. Trout KK, Homko CJ, Wetzel-Effinger L, et al. Macronutrient composition or social determinants? Impact on infant outcomes with gestational diabetes mellitus. *Diabetes Spectr*. 2016;29(2):71-78.
19. Brankston GN, Mitchell BF, Ryan EA, Okun NB. Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus. *Am J Obstet Gynecol*. 2004;190(1):188-193.
20. Halse RE, Wallman KE, Newnham JP, Guelfi KJ. Home-based exercise training improves capillary glucose profile in women with gestational diabetes. *Med Sci Sports Exerc*. 2014;46(9):1702-1709.
21. Anjana RM, Sudha V, Lakshmi Priya N, et al. Physical activity patterns and gestational diabetes outcomes - The wings project. *Diabetes Res Clin Pract*. 2016;116:253-262.
22. Hebert MF, Ma X, Naraharasetti SB, et al; Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther*. 2009;85(6):607-614.
23. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril*. 2005;83(5):1575-1578.
24. Trout KK, Averbuch T, Barowski M. Promoting breastfeeding among obese women and women with gestational diabetes mellitus. *Curr Diab Rep*. 2011;11(1):7-12.

#### Web resource

- A. [nationalacademies.org/hmd/~media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf](http://nationalacademies.org/hmd/~media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf)

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- modified observational study. *Nutr J*. 2013;12(1):139-145.
4. Osamwonyi B, Foley C. Management of recurrent urinary tract infection in adults. *Surgery*. 2017;35(6):299-305.
5. Ablove T, Patankar M, Seo S. Prevention of recurrent urinary tract infections by intravesical administration of heparin: a pilot study. *Ther Adv Urol*. 2013;5(6):303-309.
6. Beerepoot MAJ, ter Riet G, Nys S, et al. Lactobacilli vs antibiotics to prevent urinary tract infection: a randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med*. 2012;172(9):704-712.
7. De Vita D, Giordano S. Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study. *Int Urogynecol J*. 2012;23(12):1707-1713.
8. Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*. 2014;32(1):79-84.
9. Lorenz-Gomez MF, Padilla-Fernandez B, Garcia-Criado FJ, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics. *Int Urogynecol J*. 2013;24(1):127-134.
10. Porru D, Parmigiani A, Tinelli C, et al. Oral d-mannose in recurrent urinary tract infections in women: a pilot study. *J Clin Urol*. 2014;7(3):208-213.
11. Torella M, Del Deo F, Grimaldi A, et al. Efficacy of an orally administered combination of hyaluronic acid, chondroitin sulfate, curcumin, and quercetin for the prevention of recurrent urinary tract infections in postmenopausal women. *Eur J Obstet Gynecol Reprod Biol*. 2016;207:125-128.
12. Geerlings SE, Beerepoot MAJ, Prins JM. Prevention of recurrent urinary tract infections in women. *Infect Dis Clin North Am*. 2014;28(1):135-147.
13. Vahlensieck W, Perepanova T, Bjerklund Johansen TE, et al. Management of uncomplicated recurrent urinary tract infections. *Eur Urol Suppl*. 2016;15(4):95-101.
14. Badalato G, Kaufmann M. Medical student curriculum: adult UTI. American Urological Association website. Updated July 2016. [auanet.org/education/auauniversity/medical-student-education/medical-student-curriculum/adult-uti](http://auanet.org/education/auauniversity/medical-student-education/medical-student-curriculum/adult-uti)
15. Fineout-Overholt E, Melnyk BM, Stillwell SB, Williamson KM. Critical appraisal of the evidence: Part I. *Am J Nurs*. 2010;110(7):47-52.
16. Vostalova J, Vidlar A, Simanek V, et al. Are high proanthocyanidins key to cranberry efficacy in the prevention of recurrent urinary tract infection? *Phytother Res*. 2015;29(10):1559-1567.
17. Brumbaugh AR, Mobley HL. Preventing urinary tract infection: progress toward an effective *Escherichia coli* vaccine. *Expert Rev Vaccines*. 2012;11(6):663-676.