Have you tried these innovative alternatives to antibiotics for UTI prevention?

With antibiotic resistance on the rise, it helps to know which alternative therapies have data behind them—and for which populations they have been studied.

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**CASE** Recurrent UTI and antibiotic resistance

A 53-year-old postmenopausal woman with a history of culture-proven recurrent *Escherichia coli* urinary tract infections (UTIs) presents to the clinic with symptoms of UTI. She was previously treated with a postcoital regimen of trimethoprim/sulfamethoxazole, based on sensitivities identified by culture. A past work-up of her upper and lower urinary tract was negative. You send a catheterized specimen for culture; again, *E. coli* is identified as the pathogen but proves resistant to her current antibiotic regimen.

What treatment alternatives, aside from antibiotics, are available for this patient—and how might they affect resistance?

Increased antibiotic usage has led to greater bacterial resistance, which is perpetuated by clonal spread. Resistant strains of *E. coli* have been found in household members, suggesting host-host transmission as a mechanism for dissemination. Alternative treatments that reduce the use of antibiotics may minimize bacterial resistance and increase the efficacy of treatment. In the **TABLE** (page 18), we summarize alternative approaches to the treatment of recurrent UTI. We also describe a strategy to alleviate symptoms.

**Vaginal estrogen is the only proven alternative to antibiotics for postmenopausal women**

A lack of estrogen is a risk factor for UTI and is associated with atrophic mucosa, leading to decreased colonization with lactobacilli, increased vaginal pH, and *E. coli* colonization.

A randomized, double-blind, placebo-controlled trial of intravaginal estriol cream...

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versus placebo in 93 postmenopausal women found a significant decrease in the rate of UTI among women who used the cream.1 After 8 months of follow-up, the incidence of UTI was 0.5 vs 5.9 episodes per patient-year ($P < .001$). Interestingly, all pretreatment cultures were negative for lactobacilli. One month after treatment, 61% of women in the estriol group were culture-positive for lactobacilli, compared with 0% of the placebo group.1

A 2008 Cochrane review of nine studies concluded that vaginal estrogen reduces the number of UTIs in postmenopausal women, with variation based on the type of estrogen and duration of use.2

**Adverse effects are mild**

Twenty-eight percent of the estriol group in the randomized trial described above withdrew from treatment, with 20% citing local side effects, including vaginal irritation, burning, or itching—all of which were mild and self-limited.1 Other possible adverse effects include breast tenderness, vaginal bleeding or spotting, and discharge.2

**Clinical recommendations**

Given the efficacy of this therapy, we recommend topical estrogen for postmenopausal patients with recurrent UTIs.

**Cranberry juice may reduce UTI, but many patients withdraw from treatment**

Cranberries belong to the *Vaccinium* species, which contains all flavonoids, including anthocyanins and proanthocyanidins. It was previously thought that the acidification of
Urine produced an antibacterial effect, but several trials have documented no change in urine levels of hippuric acid when cranberry products are given, with no acidification of the urine. Current theory suggests that cranberries prevent bacteria from adhering to the uroepithelial cells of the walls of the bladder, by blocking expression of E. coli’s adhesion molecule, P. fimbriae, so that bacteria are unable to penetrate the mucosal surface. The major benefit of cranberry products over antibiotic prophylaxis is that they do not have the potential for resistance.

A 2008 Cochrane review concluded that cranberry juice may reduce symptomatic UTIs, particularly among young, sexually active women—but there is a high rate of withdrawal from treatment. The optimal method of administration and dose remain unclear. In contrast, two recent randomized, controlled trials—published after the Cochrane review—found no difference in the rate of recurrent UTI in premenopausal women. Adverse effects in these two trials included constipation, heartburn, loose stools, vaginal itching and dryness, and migraines. Of note, there was no statistical difference in side effects between the cranberry and placebo groups.

Vaccinium tablets may be protective in older women
Cranberry extracts of 500 mg to 1,000 mg daily have been compared with antimicrobial prophylaxis in two randomized, double-blind, controlled trials. The trials demonstrated mixed benefits. Trimethoprim/sulfamethoxazole was associated with a lower rate of UTI in younger women, compared with cranberry extracts alone (P = .02), while cranberry extracts were slightly more effective than trimethoprim alone in older women. Cranberry tablets were not associated with bacterial resistance, were cheaper, and were viewed as a more natural option. The interventions were equally well tolerated.

Overall efficacy of cranberry tablets is unclear. Side effects, albeit mild, included gastrointestinal disturbances, vaginal complaints, and rash or urticaria. There was no significant difference in the rate of adverse effects between antimicrobial treatment and cranberry tablets.

Cystopurin has not been studied
Cystopurin is an over-the-counter (OTC) tablet containing cranberry extract and potassium citrate that is taken three times daily (3 g/dose) for 2 days. Interestingly, although a proposed mechanism for the efficacy of vitamin C and cranberry juice has been a reduction of pH, potassium citrate is an alkalinizing agent that is reported to relieve burning and reduce urinary urgency and frequency. No studies have assessed this medication in the treatment of a UTI or its symptoms.
Clinical recommendations
The evidence is mixed on the use of cranberry products to reduce recurrent UTI. However, given the limited side effects associated with these products, we offer cranberry tablets to patients who have recurrent UTIs who are interested in a more natural alternative.

We generally do not recommend cranberry juice because the added fluid volume tends to exacerbate frequency and urgency symptoms.

Lactobacilli suppositories may benefit postmenopausal women
Lactobacilli are fastidious gram-positive rods and are usually the dominant component of the vaginal flora. They prevent colonization and infection by more virulent bacteria by competing for adhesion receptors and nutrients as well as producing antimicrobial substances such as hydrogen peroxide and lactic acid. A decrease in lactobacilli leaves the urinary tract susceptible to infectious organisms that may colonize the vaginal mucosa and increase the risk of recurrent UTI.

A 2008 review of randomized, controlled trials of oral lactobacilli and UTI was inconclusive, due to inconsistent dosing strategies and small sample sizes. A 2011 randomized, double-blind, placebo-controlled phase 2 trial of Lactin-V, a lactobacilli vaginal suppository, found that it reduced the rate of recurrent UTI. Lactin-V contains a hydrogen-peroxide-producing Lactobacillus crispatus developed as a probiotic that was determined to be safe and tolerable as a vaginal suppository in a phase 1 trial. The phase 2 trial enrolled 100 young premenopausal women with a history of recurrent UTI who took either Lactin-V or placebo daily for 5 days, then weekly for 10 weeks. Women in the Lactin-V group who had high levels of L. crispatus colonization experienced a significant reduction in the rate of UTI (15% vs 27% in the placebo group), but the effect did not reach statistical significance.

Little difference in adverse effects
Adverse effects were reported among 56% of patients who received Lactin-V versus 50% of those given placebo. The most common of these were vaginal discharge, itching, and moderate abdominal discomfort. Although lactobacillus can potentially promote UTI, this phenomenon is rare.

Regrettably, Lactin-V is not currently available in the United States. However, there are other lactobacilli vaginal suppositories on the market (Table, page 18). Given the low risk associated with their use, they should be considered as an alternative for patients who cannot or will not use estrogen.

Clinical recommendations
Probiotics such as lactobacilli are categorized as “dietary supplements”; as such, they are not regulated by the US Food and Drug Administration. We recommend the use of lactobacilli suppositories in postmenopausal women who have a contraindication to (or prefer to avoid) vaginal estrogen.

Skip blueberry products for now
Like cranberries, blueberries belong to the Vaccinium species and are thought to interfere with bacterial adhesion to the walls of the bladder. One in vitro trial suggests that blueberries also have antiproliferation effects, although no clinical studies have been performed to date to further investigate safety or efficacy. Consequently, we do not recommend use of these products.

Methenamine salts may benefit some populations
These anti-infective agents, including methenamine hippurate and methenamine mandelate, often are used to prevent UTI. They are found in combination OTC medications, such as Prosed DS and Urelle. Methenamine salts are bacteriostatic to all urinary tract pathogens due to their production of formaldehyde.

Although methenamine produces varying concentrations of formaldehyde,
Among pregnant women, the incidence of UTI was significantly lower in the group receiving vitamin C, compared with the control group (12.7% vs 29.1%).

Methylene blue may be useful in the elderly
Methylene blue is a light-activated compound described as “photodynamic antimicrobial chemotherapy” (PACT). Once illuminated, it becomes a bactericide, causing excitation of electrons followed by one of two reactions:
- formation of a labile singlet oxygen and then oxidation.
This makes resistance unlikely.

In an in vitro study, methylene blue was as effective as levofloxacin against Pseudomonas aeruginosa, Klebsiella pneumonia, Proteus mirabilis, Enterococcus, and Staphylococcus aureus when illuminated.

Potential benefits of this mode of treatment include local exposure and no drug interactions.

We suggest that methylene blue be placed and illuminated with a special catheter that would target UTI in the elderly population, among whom 52% of UTIs are associated with use of catheters. In vivo effects, adverse effects, and cost are not known, which limits current applicability of this compound.

Vitamin C may reduce UTI in pregnancy
The proposed mechanism for the efficacy of vitamin C for the treatment of UTI is the acidification of urine, which is believed to reduce the proliferation of bacteria. However, several studies have shown that vitamin C, at various doses, does not reliably reduce urine pH. Nonetheless, ascorbic acid was tested for its effect on UTI prevention during pregnancy.

In a single-blind trial, 110 pregnant women were divided into two groups (55 in each group):
- One group received ferrous sulfate (200 mg), folic acid (5 mg), and vitamin C (100 mg) daily for 3 months
- The other received ferrous sulfate (200 mg) and folic acid (5 mg) daily for 3 months.
Urine was cultured monthly. The incidence of UTI was significantly lower in the group receiving vitamin C (12.7%), compared with the control group (29.1%) (P = .03; odds ratio [OR], 0.35).

Uva ursi may have a prophylactic effect
Uva ursi (UVA-E) is one of the most commonly used herbal supplements for depending on the acidity of the urine, there is no evidence that acidified urine enhances methenamine’s effects.

Advantages of methenamine include the fact that it produces no changes in gut flora, poses no risk for antimicrobial resistance, and has low toxicity. It also is low in cost.

Methenamine is contraindicated in patients with renal insufficiency or severe hepatic disease.

Adverse reactions are generally mild and include gastrointestinal disturbances, skin rashes, dysuria, and microscopic hematuria.

Methenamine hippurate
A 2007 Cochrane review, deemed up to date in 2010, analyzed 13 randomized, controlled trials involving 2,032 participants. Subgroup analyses suggested that methenamine hippurate may be of some benefit to patients without renal tract abnormalities; these patients experienced significantly reduced symptoms after short-term treatment of 1 week or less.

Patients with spinal injury do not appear to benefit from treatment, according to a randomized, double-blind, placebo-controlled trial by Lee and colleagues.

Methenamine mandelate
This agent is commonly used to prevent recurrent UTI, although there is a paucity of randomized, controlled trials to support its use. One such trial in patients with neurogenic bladder found that methenamine mandelate with acidification was superior to placebo (P < .02) for preventing UTI. Beyond this population, however, it’s difficult to assess methenamine’s efficacy in the prevention of recurrent UTI.

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Methylene blue may be useful in the elderly
Methylene blue is a light-activated compound described as “photodynamic antimicrobial chemotherapy” (PACT). Once illuminated, it becomes a bactericide, causing excitation of electrons followed by one of two reactions:
- reduction oxidation
Phenazopyridine, an ingredient in several OTC medications, may exert a topical analgesic effect in women who have UTI. The crude extract from Bearberry or Arctostaphylos uva-ursi has been shown to act as an antimicrobial by decreasing bacterial adherence. In addition, investigators have found the extract to have diuretic and anti-inflammatory properties. However, few studies have explored its efficacy. One randomized, controlled trial that included 57 women (30 allocated to UVA-E and 27 to placebo) found a statistically significant reduction in the rate of recurrence at 1 year among women taking UVA-E, compared with those who did not.

Note that the women in this trial were given UVA-E for 1 month only. Long-term use of this herb has not been studied and may cause liver damage.

In a mouse model, forskolin reduced urinary-tract E. coli
This herb is derived from Indian coleus (Coleus forskohlii), a member of the mint family. It has been used primarily for its antiasthmatic, spasmolytic, and antihypertensive effects. It is believed to activate adenylyl cyclase, increasing intracellular cyclic AMP (cAMP) concentrations and activating a number of key enzymatic pathways.

The findings of a recent observational study have spurred the use of forskolin in the treatment of recurrent UTI. In the study, conducted on mice, when forskolin was injected into the bladder, intracellular E. coli decreased.

It is theorized that the incorporation of bacteria into intracellular vesicles of the bladder prevents exposure to antibiotics. When combined with an antibiotic, forskolin may increase bacterial elimination and thus lower the risk of recurrent infection. However, no randomized trials have evaluated the efficacy of this treatment.

Patients who are already taking antihypertensive medications should be cautious when using this herb, as it may lead to a drop in blood pressure.

Behavior changes are risk-free
One of the natural mechanisms that promotes bacterial elimination and prevents bacterial growth is urination. A recent review article on the subject found several contradictory studies on the effect of fluid intake on the risk of UTI. Although there is no definitive evidence that susceptibility to UTI is linked to fluid intake, adequate hydration may reduce the risk of recurrent infection.

Similarly, voiding shortly after sexual intercourse may prevent UTI. One case-control study found a modest protective effect in patients who voided after intercourse.

Clinical recommendations
Given the low risk of these measures, it seems reasonable to recommend postcoital voiding and increased fluid intake to prevent recurrent UTI.

A focus on symptoms
Phenazopyridine, the chemical found in numerous OTC medications, such as Pyridium, AZO, and Uristat, was discovered by Swiss chemist Bernhard Joos in the 1950s. Its mechanism of action is still unclear, but approximately 65% of the oral dose is excreted by the kidneys, where it has a direct topical analgesic effect.

Clinical recommendations
Patients should be warned that phenazopyridine will lead to orange urine discoloration.

The medication is generally well tolerated but should be used with caution in patients with acute renal failure, hemolytic anemia, or methemoglobinemia, as it may exacerbate these conditions.

Last words
Recurrent UTIs are common and impose a significant financial burden on our healthcare system. Although there are several antibiotic treatment options and dosing regimens available, increasing antibiotic resistance has made management of recurrent UTIs more difficult. Effective alternative
treatments that reduce the reliance on antibiotics may minimize bacterial resistance and decrease the financial burden of this common condition.

**CASE Resolved**

To reduce vaginal *E. coli*, the patient is started on vaginal estrogen cream. She is also advised to purchase cranberry tablets to help prevent future infections. Last, she is counseled about behavioral changes she can make and prescribed a short course of antibiotics to treat her culture-proven infection.

**References**

2. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens and decrease the financial burden of this common condition.