

Practical Management of Recurrent Urinary Tract Infections in Premenopausal Women

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Recurrent urinary tract infections (UTIs) are a major healthcare concern for premenopausal, healthy, sexually active women. A practical approach to the management and prevention of recurrent UTIs should be simple, practical, and cost effective. Low-dose or postcoital antimicrobial therapy can be effective for women with constellations of many recurrent UTIs, but for women with 2 to 4 UTIs per year, the most cost-effective and empowering management strategy is patient-initiated antimicrobial treatment.

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Recurrent urinary tract infections (UTIs) in premenopausal, sexually active women with anatomically normal urinary tracts are not perceived as a major clinical problem by the urology community. UTIs account for more than 7 million visits to physicians per year (1.2% of all office visits by women).¹⁻³ The financial impact of UTIs, including recurrent and uncomplicated cases, is greater than 1 billion dollars in the United States alone.⁴ Over 80% of women who

had previous UTIs have recurrent infections over the first 18 months of observation.⁵ Of these recurrent infections, three quarters are caused by reinfection with different organisms.^{6,7} Women with frequent reinfections have a rate of 0.13 to 0.22 UTIs per month (1.6 to 2.6 infections per year).^{6,7} For premenopausal, healthy, and active females, recurrent UTIs are a major healthcare concern.

Historical Management of UTIs in Women

In the 1800s, management of bladder inflammation included conservative initial treatments (bedrest, warm herbal compresses, baths, opiate-

based enemas) whereas more aggressive therapy was reserved for patients who did not improve or deteriorated during initial therapy. Aggressive treatment included mustard- or ammonia-based plasters, oral alkali, bleeding (cupping, leeches, or direct bleeding) and large doses of acid solutions.⁸ In the later 1800s, William Osler⁹ described an initial treatment consisting of absolute rest, cold applied to the loins or dry cups to the lumbar region, and amylnitrite and quinine in large doses. If these treatments were ineffective, therapy involved acetates of lead and opium, followed by ergot, gallic and tannic acid, or diluted sulphuric acid. The era of modern evidence-based urology began with the recognition that cystitis (suppuration of the bladder) was infectious in origin. Beginning in the 1900s, trials with chemotherapeutic agents such as hexamine, phenazopyridine, hexylresorcinol, and Mercurochrome¹⁰⁻¹³ were undertaken, initially with some success

and then later with some pessimism.¹⁴ Sulfanilamide, introduced in 1937, ushered in the era of modern antimicrobial therapy for UTIs.¹⁵

Has Modern Medicine Created Recurrent UTIs?

In the 1800s, a woman suffering from cystitis was bedridden for many weeks while the physician attempted to assist Mother Nature in achieving a cure. The patient usually recovered if she did not develop pyelonephritis or more complicated UTI. Felix Guyon (1831–1920)¹⁶ observed that many patients with cystitis did not experience recurrences after recovery. He proposed that this acquired

immunity was a result of autovaccination from absorption of toxins or from bacteria in a state of modified virulence. This is an interesting observation, considering that recurrence is currently a significant problem for many women, despite our broad array of very successful antimicrobial agents. Is it possible that with our modern medical practice of initiating early antimicrobial therapy for symp-

tomatic cystitis we have created the scenario of recurrent UTIs in premenopausal women? When Mabeck⁶ followed 23 untreated nonpregnant women with acute symptomatic cystitis, 21 lost their symptoms after 4 weeks (even though the bacteriuria did not disappear as quickly). However, these studies did not necessarily suggest that allowing a UTI to

clear up spontaneously changes susceptibility to recurrences. Mabeck⁶ found that 46.5% (20 of 43) of untreated patients had recurrent infections within 12 months, compared with about 40% of antimicrobial-treated patients. Similarly, Asscher and colleagues¹⁷ found that reinfections occurred in 34% of patients with asymptomatic bacteriuria treated with antibiotics, compared with 29% receiving a placebo during a 3- to 5-year follow-up. It is possible that “autoimmunity” can result from only symptomatic bacteriuria. These are interesting observations, but, unfortunately, the modern woman does not want to suffer 4 weeks of cystitic symptoms while waiting for her immune system to heal the infection.

Evaluation of Women with Recurrent UTIs

Urinalysis

Microscopy is a valuable adjunctive diagnostic tool for patients with urinary symptoms, and, if available, should be considered for patients presenting with cystitis. There are limitations in detecting microscopic bacteriuria and pyuria because of lack of standardization for the microscope itself (including magnification) and the volume of urine that can be observed, as well as if the

Urine culture is the “gold standard” for the diagnosis of UTI, although urine must be collected properly and cultured quickly or refrigerated.

urine is spun or unspun, stained or unstained. However, if microscopy is performed, the absence of pyuria should cause a physician to reconsider UTI as a diagnosis. Indirect dipstick test for bacteriuria (nitrite) or pyuria (leukocyte esterase) can be helpful. Although they are less sensitive than microscopic examination of the urine, they provide additional

confirmation of a UTI when contemplating empiric therapy and while culture results are pending.

Urine Culture

Urine culture is a standard criterion for the diagnosis of UTI, although problems exist for this "gold standard." Urine must be collected properly (mid-stream or catheterized specimen) and cultured quickly or refrigerated. Traditionally, significant bacteriuria is noted when the bacterial colony-forming unit counts reach 10⁵/mL. The problem with this somewhat

probably not necessary to repeat a urine culture at each episode. Urine culture would be mandatory, however, if the patient does not respond to empiric therapy.

Other Investigations

Many patients with recurrent UTIs are referred for urologic opinion and subsequently undergo both radiologic investigations and cystoscopy. Radiologic studies are unnecessary for the evaluation of the healthy, sexually active, premenopausal woman.¹⁸ Similarly, cystoscopy rarely will detect

always be the most appropriate screening procedures.

Traditional Management of Recurrent UTIs

Traditionally, it was taught that significant bacteriuria had to be confirmed by culture before antibiotics were prescribed. Employing this traditional approach, each UTI episode in young women was associated on average with 6.1 days of symptoms, 2.4 days of restricted activity, 1.2 days of not attending work or school, and 0.4 days of bedrest.¹⁹ Although many teachers adhere to this traditional approach (perhaps based on a misguided evidence-based criterion, FDA guidelines, or interpretation of cost-benefit ratios), most physicians will treat an uncomplicated UTI with antibiotics, based on a description of the patient's symptoms, particularly if confirmed by urinalysis (either microscopy or nitrite/leukocyte esterase dipstick) (Figure 1).

First-line therapy for acute uncomplicated cystitis in women includes nitrofurantoin (the macrocrystalline preparation is better tolerated), trimethoprim-sulphamethoxazole (TMP-SMX), trimethoprim (TMP) alone, or a fluoroquinolone (particularly in areas where TMP-SMX resistance rates approach 20%). Three days of therapy appears to be optimal because it results in similar cure rates but with decreased costs and fewer side effects compared with 7–10 days of therapy, and lower recurrence rates compared with single-dose therapy (reviewed by Schaeffer.)²⁰

Prevention of Recurrent UTIs

Conservative Approach to Prevention

A number of risk factors, other than sexual activity, have been identified in patients with recurrent UTIs. Contraceptive methods employing a diaphragm and/or spermicides (including spermicide-covered condoms) and

Renal ultrasonography is the preferred urinary tract screening imaging technique because it is noninvasive, easy to perform, and relatively inexpensive.

artificial cutoff is that many women with symptomatic UTIs present with much lower bacterial counts (such as 10²/mL), whereas patients with asymptomatic bacteriuria can have much higher counts.

Should Cultures Be Performed at

All in Women With Recurrent UTIs?

Because there are many inherent limitations and inaccuracies in urine collection and culture results, one has to carefully evaluate the rationale for obtaining a urine culture in all patients presenting with simple uncomplicated cystitis. As will be noted later in this article, a clinical diagnosis of UTI is based on symptoms, and empiric therapy with modern antibiotics is extremely successful. It can be argued that it would be cost effective in patients with recurrent UTIs to first establish the presence of significant bacteriuria associated with an episode of symptomatic cystitis, and then document that both symptoms and bacteriuria resolve with antimicrobial therapy. Once this has been confirmed in a specific patient, it is

significant pathology that would change the outcome of therapy.¹⁸ However, further investigations are important if a patient is believed to have any of the following: hematuria, a complicated UTI suggested by a history of calculi, obstruction (upper or lower urinary tract), neuropathic bladder, recent genitourinary surgery or catheterization, unusual organisms (such as tuberculosis, fungus, or urea-splitting organisms), compromised immune system, diabetes, or renal failure. Similarly, investigations are required in patients who do not respond to appropriate antimicrobial therapy after 5 to 6 days of treatment. The excretory urogram has been the traditional routine examination method of evaluating patients with complicated UTI and although it remains useful, it is not the ideal screening test today. Currently, renal ultrasonography is the preferred urinary tract imaging technique because it is noninvasive, easy to perform, and relatively inexpensive. CT and MRI offer the best anatomical detail, but because of cost they may not

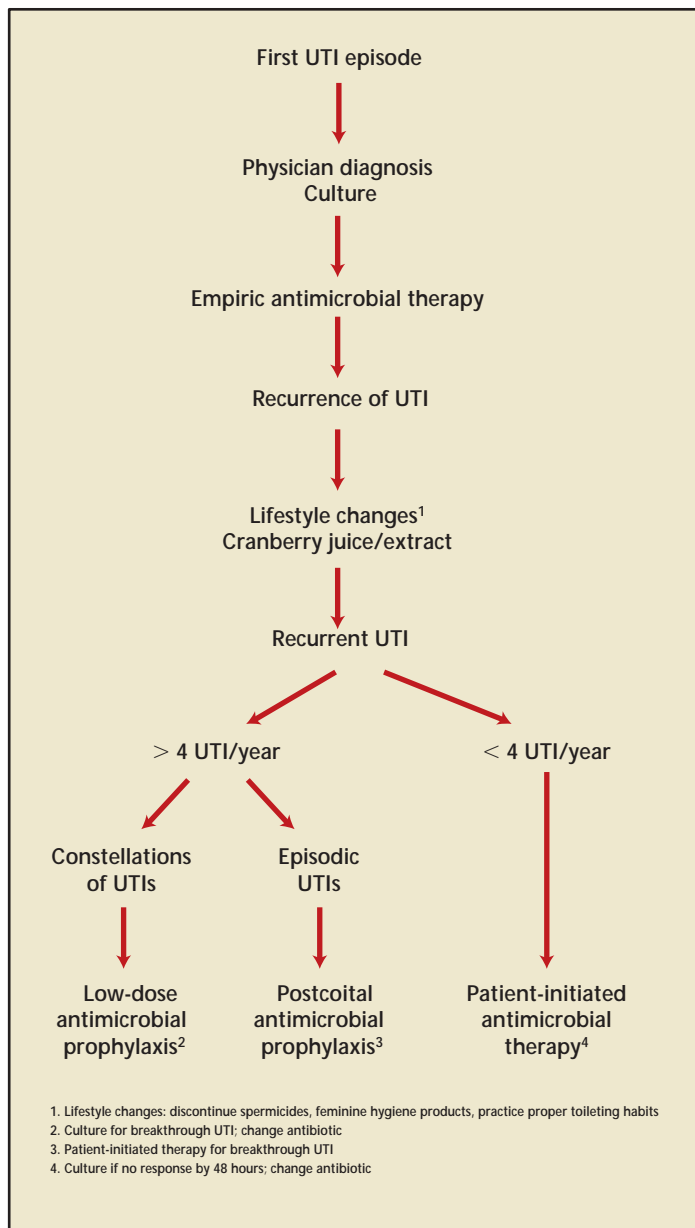


Figure 1. A proposed treatment algorithm for premenopausal women presenting with recurrent urinary tract infection (UTI).

practices (see Table 1) has proven to be effective in reducing the incidence of recurrent UTIs.

Antimicrobial Prophylaxis

The 2 contemporary strategies employing a prophylactic antibiotic regime to prevent recurrent UTIs include long-term low-dose prophylactic antimicrobial treatment or postcoital antibiotic treatment. However, it does not appear that these strategies alter the long-term risk of recurrence. Patients with frequent UTIs who take prophylactic antimicrobial agents for extended periods (for example, as long as 6 months) decrease their infections during prophylaxis, but the rate of infection returns to pre-treatment rates when prophylaxis is stopped.^{26,27} Long-term antibiotics do not appear to alter the patient's basic susceptibility to infections.²⁰

Antimicrobial agents used for long-term low-dose prophylaxis include TMP-SMX (or TMP alone), nitrofurantoin, cephalexin, and the fluoroquinolones. The dose is usually about a quarter the usual daily dose. Nitrofurantoin (because of rapid absorption in the upper intestinal tract) produces minimal fecal resistance and less vaginitis. It is, however, associated with more adverse reactions (eg, acute pulmonary reactions, allergic reactions, liver problems). Most of these long-term adverse reactions occur in older patients. TMP-SMX is a powerful prophylactic agent in preventing reinfections in the female by clearing *E. coli* from the rectal and vaginal flora, but can be poorly tolerated with potentially life-threatening side effects and the development of TMP-SMX resistant strains within the gut flora. Fluoroquinolones are probably the most effective agent for UTI prophylaxis but should probably be restricted to women with acute symptomatic cystitis in which there is significant antimicrobial resistance or to

tampon use have been associated with increased risk of UTI.^{21,22} Contraceptive methods should be changed, spermicidal agents should be discontinued, and patients should consider using pads instead of tampons. Drinking cranberry juice or cranberry extract appears to be a safe and possibly effective method of reducing the frequency of recurrent UTIs in some women.²³ Attempting to change the vaginal flora by douching with lac-

tobacilli has been suggested but not proven.²⁴ It is probable that in the future, some form of immunization program will be the key to prevention of recurrent UTIs.²⁵ It is probably appropriate to suggest that patients stay hydrated, void regularly, avoid feminine hygiene products such as vaginal douches and scented bubble baths, and practice proper toilet habits (including early postcoital voiding), although none of these

patients with intolerance to TMP-SMX, TMP, or nitrofurantoin. Nicolle and Ronald²⁸ summarized the effectiveness of prophylactic therapy in the management of women with recurrent UTIs and noted that recurrences during prophylaxis are decreased by 95%.

Acute cystitis is more common in sexually active women and a number of studies have shown that postintercourse therapy with antimicrobials such as nitrofurantoin, cephalexin, and TMP-SMX taken as a single dose effectively reduces the incidence of reinfection.^{29,30} The rationale behind postintercourse therapy²⁷ is based on the fact that intercourse results in the introduction of bacteria from the urethra into the bladder. In the absence of voiding, the bacteria grow after overnight incubation to the point where voiding and other host defense mechanisms do not eradicate them. An antibiotic taken immediately after intercourse presumably kills or arrests the growth of sensitive bacteria before they reach the critical concentration required to establish an infec-

An antibiotic taken immediately after intercourse presumably kills or arrests the growth of sensitive bacteria before they establish an infection.

tion in a susceptible individual. This approach appears to be efficacious, cost effective, and well tolerated by patients. In a placebo-controlled trial,³⁰ the infection rate observed with postcoital TMP-SMX was 0.3 per patient-year compared with 3.6 per patient-year in placebo-treated women. Depending on frequency of intercourse, postcoital prophylaxis usually results in less antibiotic use than does continuous low-dose antimicrobial prophylaxis.

Patient-Directed Self-Treatment of Recurrent UTIs

Wong and colleagues³¹ compared the

Conservative lifestyle changes (see text)
Cranberry juice/extract prophylactic therapy
Physician-directed episodic antimicrobial therapy
Low-dose prophylactic antimicrobial therapy
Postcoital prophylactic antimicrobial therapy
Patient-initiated antimicrobial therapy

effectiveness and cost of patient-initiated single-dose antibiotic therapy to antibiotic prophylaxis for women with frequent UTIs. Thirty-eight women were randomized to either continuous low-dose TMP-SMX or intermittent self-administration of a single postcoital dose of TMP-SMX. The infection rate in the prophylaxis group was 0.2 UTI/patient-year versus 2.2 UTI/patient-year in the self-treatment group. This study was also important in confirming that a UTI can be diagnosed by patients. In fact,

believed that fluoroquinolones are the ideal medication for self-start therapy because of their broad spectrum of activity compared to other potential alternatives (nitrofurantoin and TMP-SMX). The culture should be brought to the office as soon as possible and if the culture is positive and the patient asymptomatic, then another culture should be performed 7 to 10 days after therapy to determine efficacy. If the patient has symptoms that do not respond initially to antimicrobial therapy, additional culture and susceptibility tests of the initial culture specimens are performed and therapy adjusted accordingly. Although this approach is scientifically and clinically sound, it may not be time- and cost-effective, and patients would be required to submit a minimum of 2 urine cultures. With success rates in excess of 95% with fluoroquinolone therapy, one might question the usefulness of cultures in women with recurrent UTIs, except, of course, in the case of patients who do not respond clinically to empiric antibiotic therapy.

Gupta and colleagues³³ allowed women to diagnose their UTIs and immediately initiate treatment with 3 days of fluoroquinolone antibiotics. To analyze the accuracy of self-diagnosis in the study, a midstream specimen of urine (MSSU) was submitted to the laboratory for culture. Repeat

35 of the 38 UTIs diagnosed by patients were confirmed by culture. Thirty of the 35 UTIs responded clinically and microbiologically to treatment. No complications occurred in any of the 5 failures.

It has been suggested that a more accurate approach to self-diagnosis and self-start therapy would be to give patients a dip slide device to culture the urine and instruct them to perform a urine culture when symptoms of UTI occur.³² The patient would then self-start a 3-day course of empiric full-dose antimicrobial therapy immediately after performing the culture. The same investigators³²

urine cultures were submitted 10 and 30 days after treatment as part of the experimental protocol. The investigators also interviewed the patients posttherapy. One hundred and seventy-two women (average age 23 years), predominantly white, unmarried, and sexually active, had at least 2 UTIs the previous year. Eighty-eight of these 172 women self-diagnosed 172 UTIs. A uropathogen was cultured in 84%, sterile pyuria was identified in 11%, and in only 5% was pyuria or bacteriuria not detected. Clinical cures (complete eradication of symptoms) were noted in 92%, microbiological cures (eradication of bacteria) were noted in 96%. There were no adverse events and almost 100% of the patients were very happy with this management plan.

A Practical Plan for Women With Recurrent UTIs

For premenopausal women with recurrent UTIs, particularly sexually active women, it may not be appropriate to continue with the "status quo" and dogmatic approach of physician-directed investigations, culture, and antibiotic prescription for each episode. Antibiotic prophylaxis is effective for women who develop

a frustrating constellation of very frequent UTIs (and it is recognized that UTIs tend to cluster in some women). Although it does not change the long-term prognosis of future UTIs, it certainly allows the patient the chance of a long period without cystitis-like symptoms. For sexually active women with frequent UTIs, postcoital antibiotic therapy appears to successfully reduce the frequency of symptomatic recurrent episodes of cystitis. For motivated and active women who suffer 2 to 4 UTIs per year, a patient-initiated treatment strategy for their recurrent UTIs should be considered. It is appropriate to make sure that at least 1 symptomatic episode of cystitis is associated with a positive culture and that patients symptomatically resolve on a 3-day course of antibiotics. Once this is established, there is evidence that women with recurrent UTIs can accurately self-diagnose and self-treat uncomplicated cystitis (as accurately as any physician). This becomes a very self-empowering treatment strategy for many women. Physicians, however, are not superfluous. A patient-initiated treatment of recurrent UTI still remains a physician-directed management strategy. This

management plan saves valuable time (for both the physician and patient), reduces expense (eg, unnecessary cultures, office visits, time off work), and allows for an early initiation of therapy with no apparent increase in treated episodes. ■

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Main Points

- Recurrent urinary tract infections (UTIs) in healthy premenopausal women are a major health concern, and UTIs account for 7 million physician visits per year at a cost of 1 billion dollars.
- Treatment of UTI in women has evolved from historically very conservative treatments, such as bedrest and herbal compresses, to current modern practices, which include use of antibiotics such as nitrofurantoin, trimethoprim-sulphamethoxazole (TMP-SMX), trimethoprim (TMP), and the oral fluoroquinolones.
- Risk factors for recurrent UTIs include use of a diaphragm and/or spermicides, and tampon use. Certain lifestyle changes are suggested to help reduce incidence of UTIs, but they have not been proven to be effective.
- Two other contemporary strategies employed in preventing recurrent UTIs are long-term low-dose prophylactic antimicrobial treatment and postcoital antibiotic treatment. These treatments have proven effective over extended periods of use (more than 6 months), but patients return to pretreatment rates of infection after prophylaxis is stopped.
- Studies have shown that patients can effectively diagnose their own UTIs and self-initiate treatments with the same success rate as physicians. This is a self-empowering strategy for many women and also helps save time and money. Physicians should still play an important management role.

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