Long-Term Prophylactic Therapy in Recurrent UTI

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Recurrent UTIs: A prologue

Urinary tract infections (UTIs) are one of the most common infections observed in the primary care.[1] The infection is seen more often in women than in men (8:1), with approximately 50-60% of women reporting at least one incidence in their lifetime; majority in the third and ninth decades.[2,3] Recurrence after UTIs is common in adult women.[4] Recurrent UTIs, including relapses and reinfection, are defined as ≥2 uncomplicated UTIs in the past 6 months, or ≥3 infections within the preceding year (Figure 1).[5] In a primary care setting, 53% of women above the age of 55 years and 36% of younger women report a recurrence within 1 year.[6]

The most dominant organism in UTIs is reported to be uropathogenic *Escherichia coli (E. coli)* (UPEC). Its dominance can be attributed to the proximity of the urethra to the intestine, particularly in catheterized patients. Other causative organisms include *Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus saprophyticus,* and *Enterococci fecalis* and *fecium*. All of these uropathogens express virulence factors (pili, adhesins, toxins, capsules biofilms etc.) that aid in colonization and invasion of the urinary tract (Figure 2).[7]

Factors increasing the recurrence of UTIs in women

There are certain factors that predispose women to recurrent UTI. These factors are different for pre- and post-menopausal women, and are depicted in Figure 3. The predominant factors in pre-menopausal women include frequency of sexual intercourse, new partners, use of spermicide and diaphragm use. All of these risk factors have been found to increase vaginal and urethral colonization with *E. coli.* For postmenopausal women, the risk factors include estrogen deficiency, cystocele, urogenital surgery, high post-void residual volume and a previous UTI. The post-menopausal women also have a relative depletion of vaginal lactobacilli and an increase in vaginal *E. coli* compared with premenopausal women.[1,6]

Evaluation of women with recurrent UTIs

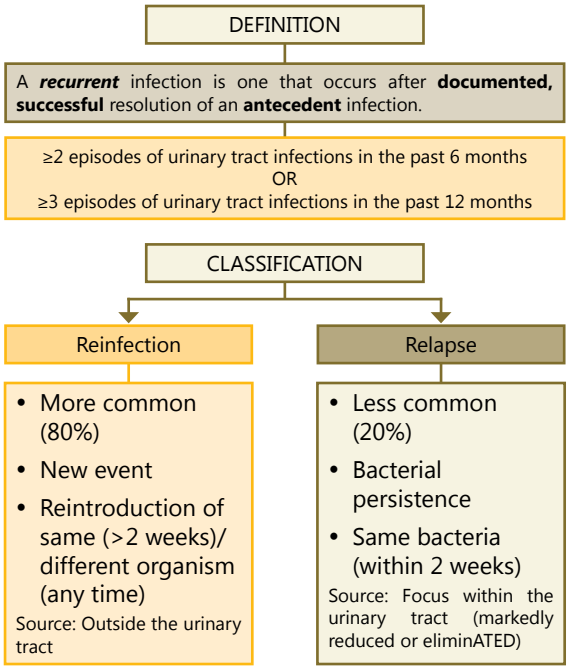
Urinalysis

Microscopy is considered as a useful adjunct for diagnosis in these patients. However, there are some limitations in detecting microscopic bacteriuria and pyuria due to lack of standardization for the microscope itself (including magnification) and the volume of urine that can be observed, as well as if the urine is spun or unspun, stained or unstained.[8]

Urine culture

Urine culture and sensitivity testing are the standard diagnostic criteria to detect the causative organism and to decide the type of antimicrobial therapy. A culture result

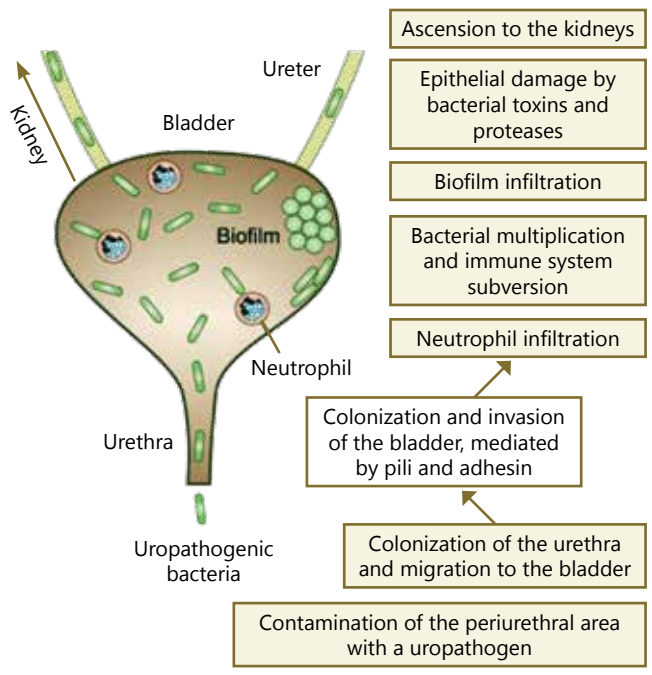
Figure 1: Recurrent UTIs



Adapted from: Jhang JF, Kuo HC. Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. *Ci Ji Yi Xue Za Zhi.* 2017;29(3):131–137.

is positive for a UTI when there are greater than 100,000 colony-forming units (cfu)/mL. In recurrent UTIs, a urine culture can remain positive for more than two weeks even after treatment. This investigation is a bit technique sensitive, for instance, a 'clean-catch' or midstream technique needs to be used when collecting the urine sample, which reduces the risk of vaginal and skin contamination to approximately 30%, and this sample should then be quickly cultured or refrigerated.[2,8]

Figure 2: Colonization of the bladder by uropathogenic bacteria



Adapted from: Martell JAO, Naber KG, Haddad JM, Saucedo JT, Burgos JAD. Prevention of recurrent urinary tract infections: bridging the gap between clinical practice and guidelines in Latin America. *TherAdv Urol.* 2019,11:29–40.

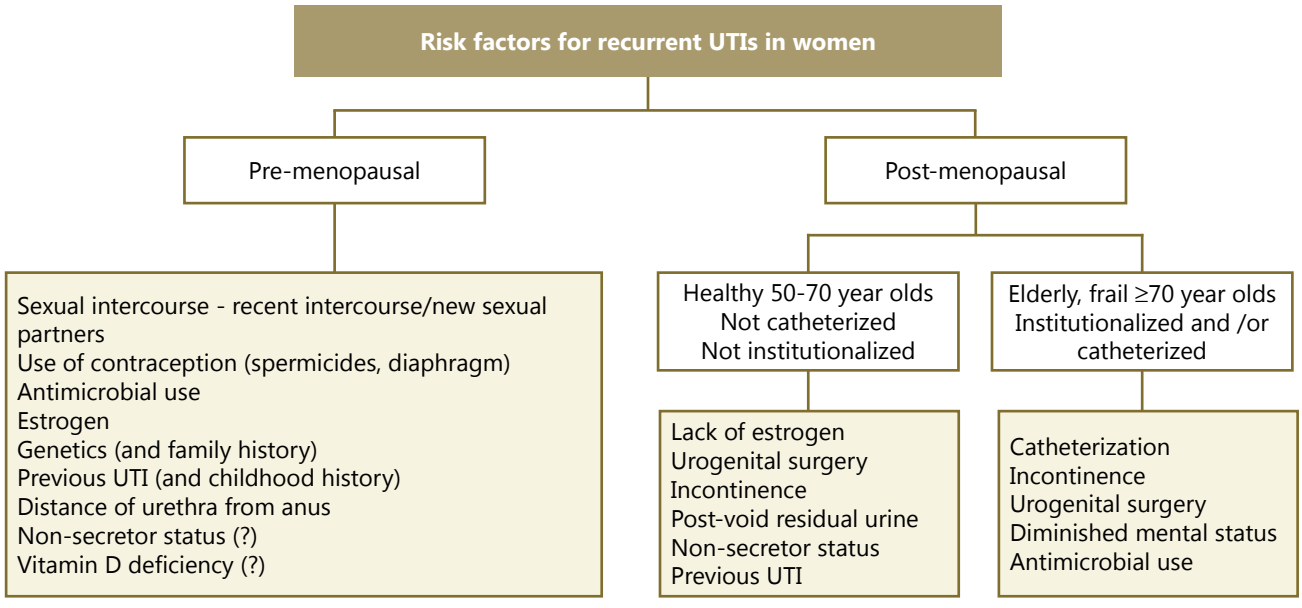
Indications for further investigation of recurrent UTIs

Patients with recurrent UTIs should be referred to a urologist if the patient has any of the following:[8,9]

- Bacterial persistence after sensitivity-based therapy
- Persistent pyuria
- Prior urinary tract surgery or trauma
- Gross hematuria before or after resolution of infection
- Previous bladder or renal calculi
- Obstructive symptoms (straining, weak stream, intermittency, hesitancy),
- Urea-splitting bacteria on culture (e.g., Proteus, Yersinia)
- 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.

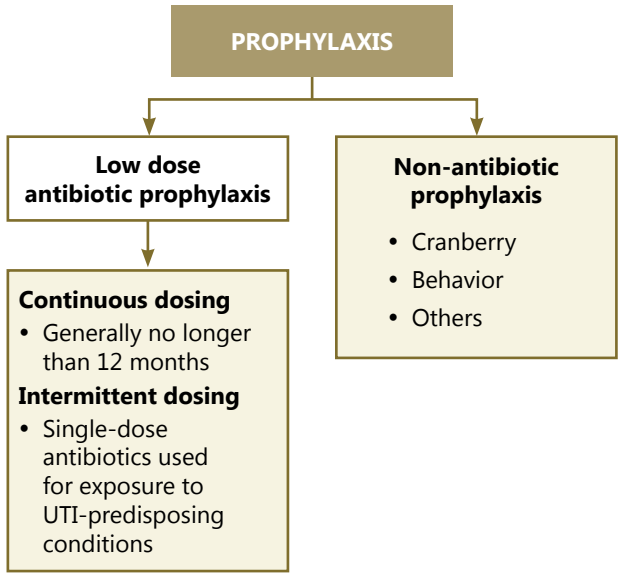
In above situation, kindly get uroflowmetry done and ultrasound KUB plus residual urine.

Figure 3: Risk factors for recurrent UTIs in women



Source: Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent urinary tract infections in women. *Int Urogynecol J.* 2015;26(6):795-804.

Figure 4: Prophylactic approaches to prevent recurrent UTIs



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If uroflowmetry shows obstruction, then patient would require urethral dilatation . If ultrasound shows significant residual urine, then patient should be catheterized. If there is any upper tract dilatation, then the cause is to be identified and treated, and then in these cases CT scan may be required for further evaluation. If uroflow is normal, and ultrasound is normal and patient has persistent pyuria in spite of treatment with no fever, investigate for genitourinary tuberculosis.[8,9]

Preventing recurrent UTIs

There are three tiers of prophylactic approaches to prevent recurrent UTIs, namely, behavioral modifications and counselling, followed by non-antibiotic prophylaxis, and finally by low-dose continuous or postcoital antibiotic prophylaxis (Figure 4).[7,10]

Conservative/non-antibiotic approach to prevention

Behavioral changes and modification of risk factors entails the conservative approach to prevent recurrent UTIs. It is suggested to the patients to maintain hydration, void regularly, avoid feminine hygiene products such as vaginal douches and scented bubble baths, practice proper toilet habits including early postcoital voiding, change the contraceptive methods, discontinue spermicidal agents, drink cranberry juice/extract, and use probiotics .[8,11]

Antibiotic prophylaxis

The pharmacological strategies used to prevent recurrent UTIs are – long-term low-dose prophylactic antimicrobial treatment and postcoital (or intermittent) antibiotic treatment. These treatments have proven effective over extended periods of use (more than 6 months), however, it should be taken into consideration that the patients return to pretreatment rates of infection after prophylaxis is stopped.[8] This approach is also supported by the recent 2019 guidelines from AUA/CUA/SUFU which suggest that clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs following discussion of the risks, benefits, and alternatives.[10]

Continuous antimicrobial prophylaxis for recurrent UTIs

Prophylaxis with extended courses of low-dose antibiotic therapy has been shown to reduce the recurrent rates by upto 80%.[3] This therapy is even effective in reducing the risk of recurrence in postmenopausal women with recurrent UTI.[12] Furthermore, continuous antibiotic prophylaxis is also effective in reducing UTI frequency in clean intermittent self-catheterization (CISC) users with recurrent UTIs, and it is well tolerated in these individuals.[13]

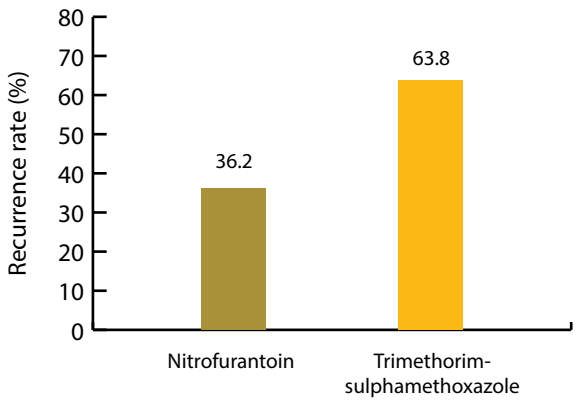
Increased resistance of urinary bacteria is however a concern that requires surveillance if prophylaxis is started.[13] Additionally, patients on long-term prophylaxis should be informed about the possible side-effects with this therapy, with advice to seek medical attention if they occur.[14]

Role of nitrofurantoin in prophylaxis for recurrent UTIs

Nitrofurantoin is one of the drug-of-choice used in the management of UTIs, including prophylaxis or long-term suppressive therapy for recurrent UTIs. Especially in the hour of increasing antibiotic resistance, nitrofurantoin has been observed to be a suitable candidate for the treatment of infections caused by multidrug-resistant pathogens.[15] Nitrofurantoin susceptibility in bacteria correlates with the presence of bacterial nitroreductases which convert nitrofurantoin to highly reactive electrophilic intermediates. These intermediates attack bacterial ribosomal proteins non-specifically, causing complete inhibition of protein synthesis.[16]

Nitrofurantoin has a wide range of action against a variety of Gram-positive and Gram-negative organisms. It is bactericidal against most common urinary tract pathogens, including *E coli,* Enterococci, Klebsiella, *Staphylococcus saprophyticus,* and Enterobacter. Its spectrum of susceptibility

Figure 5: Efficacy of nitrofurantoin versus trimethoprim-sulphamethoxazole in preventing recurrent UTIs



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also includes Shigella, Salmonella, Citrobacter, Neisseria, Bacteroides, group B streptococcus, *Staphylococcus aureus,* and *Staphylococcus epidermidis*. A major advantage is that resistance to this agent remains relatively rare despite several decades of widespread use. Another advantage is that it concentrates in the lower urinary tract while maintaining a low serum concentration and also does not significantly affect bowel flora.[17]

Its efficacy as a prophylactic agent in recurrent UTI management is well-supported by a plethora of clinical evidences. Nitrofurantoin has been found to be as efficacious as other antimicrobials as reported in systematic review and meta-analyses done by Price *et al*[18] and Muller *et al*[19]. In a study done to compare prophylactic effect of nitrofurantoin and trimethoprim-sulphamethoxazole (TMP-SMX) in recurrent UTIs in children and to determine antibiotic resistance pattern while receiving prophylaxis, it was found that nitrofurantoin was more effective than TMP-SMX in preventing recurrent UTI (Figure 5). Also, it (37.5%) caused less emergence of resistance bacteria than TMP-SMX (56%).[20]

Conclusion

Recurrent UTIs are common in women and associated with considerable morbidity and health care use. The clinical manifestations, diagnostic tests and causative organisms are usually similar to those of single case of UTI, although the treatment strategies and preventive measures might be slightly different. Antimicrobial prophylaxis has proved effective in reducing the risk of recurrent UTIs. Amongst the recommended antibiotics for prophylaxis, nitrofurantoin has emerged as a beneficial agent owing to its spectrum of action, even against the multidrug resistant pathogens.

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